

PATHOGENETIC ROLE OF VITAMIN D AND ANTIMICROBIAL PEPTIDES IN FORMATION OF RECURRENT BRONCHITIS IN CHILDREN

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ABSTRACT

The analysis of the maintenance of a metabolite of vitamin D (25-dihydroxyvitamin D) in blood serum and level α -defensin 1-3 in sick children's blood plasma with recurrent bronchitis was carried out. It is established that children with recurrent bronchitis reliable decrease in blood serum of concentration of a 25-dihydroxyvitamin D and increase of the contents of antimicrobial peptide cathelicidin LL-37. Decrease of the plasma level of metabolites of vitamin D in children with a recurrent bronchitis accompanies by increase of the contents of the α -defensins 1-3 in blood plasma and that could act as a padding factor of a relapsing course of a disease. The finding is a substantiation for inclusion of vitamin D in complex therapy of children with recurrent bronchitis.

Keywords: vitamin D, Vitamin-D-Bindungsprotein, cathelicidin, α - defensins 1-3, recurrent bronchitis, children.

The researches of different years contain indisputable proofs of essential changes of nonspecific protection of an organism and the immune status in the patients having diseases of respiratory organs. Slow character of an inflammation and its transition to the chronic can be connected with inferiority of cells effectors of an inflammation – neutrophils and macrophages. Among the modern researches there are some works on the influence of vitamin D on a condition of immunity [1, 2, 3] that allowed essentiality to review the physiological value of this vitamin [4]. The important functional role of D3 vitamin in the immune answer of an organism indicate the existence of receptors to its hormonal forms in immunocompetent cells, and also that fact that some of these cells are capable to synthesize the fissile metabolites of D3 vitamin [5].

Inflammatory diseases of a respiratory passage are often connected to the violations of synthesis of antimicrobial peptides as the representative one of which is defensins [6]. During the development of immune system defensins had the special immune regulated role. On the one hand, defensins possess anti-inflammatory properties due to the induction of secretion of interleukin-10. On the other hand, defensins send neutrophils, V-cells, macrophages to the inflammatory area, it leads to the release of inflammatory mediators, such as interleukin-8, interleukin-6, interleukin-10, interferon- γ and interleukin of B4 [7, 8, 9]. Thus, defensins act not only as endogenic antibiotics, they also play an important role in the activation of processes of an inflammation, reparation and regulation of adaptive of the immune reaction [10, 11] The violation of an expression of defensins is followed by increase of risk of development of infectious, inflammatory, allergic and autoimmune diseases [10].

The synergetic antibacterial effect with defensins has another antimicrobial peptide; it is cathelicidin (LL-37) [12]. Cathelicidin LL-37 is considered as one of key molecular components of the congenital mechanisms of immunity

providing urgent protection against infections in the level of integuments, mucosa and skin [13]. LL-37 possesses a wide range of the antimicrobial activity concerning bacteria, fungi and parasites [14]. However at a direct action of microbial incentives the antimicrobial peptides are not developed in the significant amounts [15]. The expression of the person's cathelicidin, both in epithelial cells (keratinocyte), and in monocytes/macrophages occurs in response to exaltation of TLR at sufficient concentration of vitamin D [15].

Work purpose: to estimate a pathogenetic role of vitamin D and the antimicrobial peptides (α -defensins 1-3, cathelicidin) in formation of recurrent bronchitis in children.

Materials and research techniques. For the achievement of the goal the complex examination of 32 children with recurrent bronchitis in the aggravation period aged from 5 till 10 years is conducted (average age of patients made $6,4 \pm 1,3$ years). The obligatory complex of examination included a chest X-ray, research of clinical blood analysis, clinical urine analysis. The control group was made by 30 healthy children, representative on age and gender.

The research of a 25-dihydroxyvitamin D, vitamin-D-bindungsprotein, a cathelicidin LL-37, α -defensins 1-3 was carried out by the method of an enzyme immunoassay with the use of the commercial sets of dough IDS OSTEIA 25-Hydroxy Vitamin D, Vitamin-D-Bindungsprotein (ELISA Kit). LL37 (Human, ELISA), HNP 1-3 (ELISA, Bio Tech Lab-S) respectively.

The received results are processed by the method of variation statistics with the use of a package of the analysis of the Statistic for WINDOWS 6.0 program with the function of calculation of an arithmetic average (M), an average quadratic deviation (σ) and average mistakes (m). For an assessment of distinctions of indexes in the compared groups the student's criterion was used. The distinctions considered reliable at $p < 0,05$.

Results and discussion

The carried-out analysis of the maintenance of metabolites of vitamin D in blood serum, it is revealed that concentration of a 25-dihydroxyvitamin D in children with recurrent bronchitis

was 1,6 times lower in comparison with healthy children and made $60,8 \pm 2,69$ MME/ml against $99,9 \pm 4,3$ MME/ml, respectively ($p < 0,05$) (table 1).

Table 1

The maintenance of metabolites of 25-dihydroxyvitamin D, vitamin-D-bindungsprotein, antimicrobial proteins in children's blood serum with recurrent bronchitis (M±m)

Parameters	Recurrent bronchitis, n=32	Healthy controls, n=30	p-values
25-dihydroxyvitamin D, MME/ml	$60,8 \pm 2,69$	$99,9 \pm 4,3$	$< 0,05$
Vitamin-D-bindungsprotein, ng/ml	$59,90 \pm 3,41$	$68,33 \pm 4,02$	$> 0,05$
Cathelicidin LL-37, ng/ml	$0,1 \pm 0,01$	$0,3 \pm 0,09$	$< 0,05$
α-defensins 1-3, pg/ml	$6576,7 \pm 602,8$	$3583,3 \pm 735,4$	$< 0,05$

In view of that fact that deficiency of vitamin D is followed by the development of a secondary immune failure which is shown by decrease in phagocytic activity of cells, decrease of production of an interferon, delay of processes of synthesis of interleukin 1 and 2 [4, 16, 17], it is possible to assume that the decrease of the activity of metabolites of vitamin D in children's blood serum of a basic group acts as one of factors formation of a recurrent disease. The data obtained by us coincide with the results of a number of researches which specify that poor security of an organism with vitamin D correlates with frequent infectious diseases, including with a high level of respiratory diseases [18, 19].

It is known that vitamin D is biologically inactive. A necessary condition of performance by vitamin D of the functions is its serial turning in liver and kidneys with formation of a 25-dihydroxyvitamin D3 (25D) and 1,25D or 24,25-dihydroxyvitamin D3 (24,25D) [20, 12-18]. The formed vitamin D communicates generally with vitamin-D-bindungsprotein and in such look is transported by the circulating blood at first into liver, and then into kidneys where there is a terminating activation of vitamin D in 1,25-dihydroxyvitamin D which is a terminating and most fissile metabolite of vitamin D [21, 22]. A trial function vitamin - D - the connecting protein is transport of Calciferol and vitamin D to cells targets [23]. In this regard the level of vitamin-D-bindungsprotein in blood serum is the reliable indicator of the maintenance of vitamin D in an organism, and the poor quantity vitamin-D-bindungsprotein can be the cause of the development of endogenic deficiency of vitamin D even on condition of its sufficient exogenesis receipt in an organism [20] The level in children's blood serum of groups of supervision vitamin-D-bindungsprotein was studied. By results of research the tendency to decrease of vitamin-D-bindungsprotein in children with recurrent bronchitis which level in blood serum made $59,90 \pm 3,41$ ng/ml against $68,33 \pm 4,02$ ng/ml in children of control group is established ($p > 0,05$).

It is proved that the influence of vitamin D on immune system is mediated by its ability to induce an expression of peptides with strong antibiotic effect, such as defensins and a cathelicidin [24]. In turn, the antimicrobial peptides (cathelicidin and defensins) not only show microbicide action, but also can act as the alarm molecules activating immune system. Action of antimicrobial peptides leads, mainly, to

violation of structure and function of a cytoplasmatic membrane of microorganisms, changes a transmembrane transmittivity that, in turn, causes a progreduated demineralization of a cell and leads to the death of a microorganism [11, 25]. This fact explains the padding mechanism of influence of vitamin D on the acquired (adaptive) immunity [26].

The following stage of studying was the research of the maintenance of a cathelicidin LL-37 in children's blood serum with recurrent bronchitis. By the results of research it was established that the maintenance of LL-37 in patients with recurrent bronchitis was 3 times lower, than in control group and made

$0,1 \pm 0,01$ ng/ml against $0,3 \pm 0,09$ ng/ml, respectively ($p < 0,05$). Considering that synthesis of LL-37 is mediated by vitamin D, we defined coefficient of a equilibration of LL-37 and 25-dihydroxyvitamin D. It is found that in the group of children with recurrent bronchitis in comparison with control group was noted not only the lowered maintenance of a cathelicidin, but also its equilibration with vitamin D ($0,16 \pm 0,02\%$ against $0,44 \pm 0,12\%$, respectively, $p < 0,05$). That is low levels of vitamin D in children with recurrent bronchitis do not provide activation of synthesis of LL-37. In view of a role of a cathelicidin LL-37 in realization of the antimicrobial protection of an organism and a failure of its synthesis in children from group of supervision in combination with the available deficiency of vitamin D, it is possible to come to a conclusion about the pathogenetic role of these factors in the recurrent disease.

With underlying it is established that level α-defensins 1-3 in children's blood plasma with recurrent bronchitis exceeded results of control group almost twice and made $6576,7 \pm 602,8$ pg/ml against $3583,3 \pm 735,4$ pg/ml, respectively ($p < 0,01$). It is possible to assume that activation of synthesis of the specified antimicrobial peptides is compensatory reaction in response to poor synthesis of a catheliticidin and vitamin D. It is known that the high maintenance of antimicrobial peptides in the circulating blood reduces number of exacerbations of a bacteriemic infection and provides more mild course of a disease [11]. At the same time there is an instruction that high levels α-defensin induce a release interleukin-8 and a neutrophil - activating protein 78 of epithelial cells of airways that leads to padding migration of polymorphonuclear leukocytes in the center of an inflammation [27]. Besides,

α -defensins 1-3 in high concentration increase permeability of a microcirculatory flow as directly, and by stimulation of degranulate of mast cells. [11, 28]. That is in such conditions the compensatory and adaptation reaction directed on overcoming of a contamination of pathogen accepts character pathological and acts as a padding factor of defeat of respiratory system and the recurrent disease.

Summarizing above explained, it is possible to assume that as the possible reason and a release of a recurrent bronchitis in children acts the deficiency of vitamin D associated with an imbalance in system of the antimicrobial peptides. Above the explained acts as pathogenetic background of need of prolongation of the period of the exogenous donation of vitamin D.

Conclusions

1. As one of pathogenetic mechanisms of development of an exacerbation of recurrent bronchitis in children deficiency of a 25-dihydroxyvitamin D and the antimicrobial peptide of a cathelicidin LL-37 acts.

2. Decrease in level of a metabolite vitamin D in children's blood serum with recurrent bronchitis, is followed by compensatory increase of the maintenance in a blood plasma α -defensins 1-3 that acts as a padding factor of a recurrent disease.

3. The reached data act as the background for the consideration the of the question inclusion in children's complex therapy of with recurrent bronchitis of vitamin D.

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ОРГАНИЗАЦИЯ ПОМОЩИ БОЛЬНЫМ МУКОВИСЦИДОЗОМ В СТАВРОПОЛЬСКОМ КРАЕ

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ORGANIZATION OF AID BY SICK CYSTIC FIBROSIS IN STAVROPOL TERRITORY

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АННОТАЦИЯ

В 2014 году в Российский регистр больных муковисцидозом внесены данные о пациентах, проживающих в Ставропольском крае для участия в регистре европейского общества муковисцидоза (ECFS). Введение и анализ регистра больных муковисцидозом Ставропольского края позволили выявить особенности течения заболевания, уточнить генетическую характеристику больных, их микробиологический профиль. Благодаря регистру разработаны соответствующие программы диагностики, стандартизирована медицинская помощь, усовершенствована система диспансеризации и реабилитации пациентов.

ABSTRACT

In 2014 the year into the Russian register of the patients with cystic fibrosis are introduced the data about the patients, who live in