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ASSESSMENT OF SEVERITY OF CYSTIC FIBROSIS IN CHILDREN DEPENDING ON THE VITAMIN D STATUS

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Abstract

Introduction

Severity of CF depends on speed of lung disease progression which depend on many factors. Patients with CF suffer from vitamin D deficiency that could contribute to decreasing of lung function due to anti-inflammatory and antimicrobial activity. Correction of vitamin D_3 level may be a potentially effective way to keep pulmonary function in such patients.

Purpose. Evaluation of severity of CF in children depending on the vitamin D_3 level in blood serum.

Materials and methods. 84 children suffering from CF have been examined. Level of 25 (OH) D_3 in blood serum measured with immunosorbent assay. Patients were performed spirometry and the bacteriograms of sputum coughed up by children were analyzed.

Results. Measurement of serum vitamin D_3 among children with cystic fibrosis showed that 58,3% of subjects had insufficiency. Children who suffered from severe CF had significant lower serum 25 (OH) D_3 concentrations. It was shown that children with insufficient level of 25 (OH) D_3 had higher risk of FEV_1 rate decreasing less than 64 %, and significant

association with *Ps. aeruginosa*-positive culture was detected. Subjects with sufficient 25 (OH) D_3 had strong association with higher rates of FEV_1 and risk of *Ps. aeruginosa*-positive culture was also decreased.

Conclusions. Vitamin D insufficiency is common among children with cystic fibrosis. It was found that there is a relationship between the content of 25 (OH) D_3 and the severity of the disease. Children with low levels of 25 (OH) D_3 are associated with lower FEV1 rates and have a higher risk of positive culture of *Ps. aeruginosa.*

Key words: cystic fibrosis; children; vitamin D; severity of the disease.

Introduction

Cystic fibrosis (CF) is a hereditary genetic autosomal recessive disease caused by CFTR gene-mutation, a protein that functions as chloride channel. Progressive lung affection and exocrine pancreatic insufficiency are dominant manifestations of the disease. Severity of CF depends mostly on speed of pulmonary manifestations progression which in their turn depend on bacterial infection, nutritional status, character and effectiveness of treatment and individual factors [3].

Patients with CF often suffer from vitamin D deficiency [**Error! Reference source not found.**] which is caused by a number of reasons and associated with failure in regulation of inflammatory response in respiratory tracts, tendency to infectious complications and deterioration of pulmonary function [**Error! Reference source not found.**]. It has been known that vitamin D plays a critical role in activation of antimicrobial protection and takes part in regulation and coordination of a lot of processes, including immune and inflammatory response. Immune response induced by vitamin D through VDR (the vitamin D receptors), stimulate a number of genes which code antimicrobial proteins such as cathelicidins, defensins, hepcidins and neutrophil peptides which act as antibiotics against various pathogens [1].

Anti-inflammatory and antimicrobial activity of vitamin D_3 in patients with CF is of particular interest as it is a potentially effective way to keep pulmonary function in such patients. Research on the relationship between patients' status with CF and level 25 (OH) D_3 in blood serum still constitutes a topical issue.

Purpose. Evaluation of severity of CF in children depending on the vitamin D_3 level in blood serum.

Materials and research methods

84 children suffering from CF have been examined by us. Verification of diagnosis was performed in accordance with recommendations on diagnosis of CF by American Cystic Fibrosis Foundation «Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation» [2]. We have assessed all patients' anamnesis: their complaints, life history and course of disease as well as the results of objective testing and instrumental examination. The assessment of the severity of disease was done according to Shwachman–Brasfield scale.

All children of the examined group were measured the level of 25-Hydroxycholecalciferol (25 (OH) D_3) in blood serum with immunosorbent assay "25-OH-Vitamin D-ELISA" (BioVendor, Germany). The measurement of level 25 (OH) D_3 was carried according to the referential meanings and met the following criteria: 30 – 50 ng/ml – sufficient level, 20 - 30 ng/ml – insufficient level, below 20 ng/ml – deficit of vitamin D_3.

Patients who had attained the age of 5 years and could follow the researcher's instructions were performed spirometry and assessed the function of external respiration (n = 80). The following parameters were evaluated: FVC (forced vital capacity), PEF (peak expiratory flow), index Tiffeneau, MEF 25%, MEF 50%, MEF 75% (maximal expiratory flow at the level of expiration 25%, 50% and 75% FVC) and FEV_1 (forced expiratory volume during the first second). The main indicator of severity of pulmonary manifestations was FEV_1 ratio as the most significant factor [3], and it was interpreted as «normal» if was 80 % and more, 65 - 79 % - «moderate violation», 64 % and less – as «severe violation».

Moreover, we have analyzed the bacteriograms of sputum coughed up by children with CF as of examination.

The results of the research have been statistically processed with the help of statistical system «IBM SPSS Statistics» Version 12 (20) using parametric and nonparametric methods and ROC-analysis.

Results and discussion

General characteristics of the examined group see in Table 1.

Among all subjects 58,3 % were vitamin D insufficient. The mean serum 25(OH)D_3 concentration for the entire cohort was 28,98 ± 0,78 ng/ml (girls - 29,08 ± 1,27 ng/ml, boys - 28,90 ± 0,98 ng/ml). Assessment of 25(OH)D_3 levels between children with different severity of the disease showed substantial differences between children with severe, moderate and

mild CF. The mean serum 25(OH)D_3 concentration in subjects with severe CF was 24,23 ± 0,81 ng/ml, that is significantly lower from moderate CF (30,32 ± 0,83 ng/ml, $p \leq 0,001$) and mild CF (38,91 ± 2,18 ng/ml, $p \leq 0,001$).

Table 1 - Characteristics of the examined group

	Boys	**Girls**	**Total**
	n (%)	n (%)	
Age	10,63 ± 0,58	8,54 ± 0,74	9,71 ± 4,33
Sex	47 (55,95%)	37 (44,05%)	84 (100%)
Pancreas function:			
- pancreatic sufficient	1 (2,13%)	1 (2,70%)	2 (2,38%)
- pancreatic insufficient	46 (97,87%)	36 (97,30%)	82 (97,62%)
Course of CF:			
- severe	21 (47,7%)	13 (35,1%)	34 (40,5%)
- moderate	21 (44,7%)	18 (48,6%)	39 (46,4%)
- mild	5 (10,6%)	6 (16,2 %)	11 (13,1 %)
Mutation:			
- F508del/ F508del	20 (42,6%)	17 (45,9%)	37 (44,0%)
- F508del/other mutation	19 (40,4%)	15 (40,5%)	34 (40,5%)
- other mutations	8 (17,0%)	5 (13,5%)	13(15,5%)

Evaluation of FEV1 measurements found considerable differences between children with severe, moderate and mild CF. The average rate of FEV1 in subjects with severe form of the disease was 72,34 ± 2,70 % ($p \leq 0,01$), in moderate group 77,68 ± 2,91 % ($p \leq 0,05$), comparatively to mild CF (91,50 ± 4,08 %).

Collected microbiology results were analyzed and it was revealed, that subjects had positive culture for *St.aureus* (54,8 %), *Ps. aeruginosa* (38,1 %), *Str. pyogenes* (33,3 %), *Str. viridans* (45,2 %), *Str. agalactiae* (10,7 %), *C. albicans* (56,0 %) and *Enterococcus spp.* (41,7%).

Patients with severe CF exhibited significant bacterial colonization, including St. aureus (67,6 %), Ps. aeruginosa (52,9 %), Str. agalactiae (20,6 %), Enterococcus spp (44,1 %), which contrasted with moderate CF (St. aureus 43,6 %, Ps. aeruginosa 33,3 %, Str. agalactiae 17,7 %, Enterococcus spp 43,6 %) and mild CF (St. aureus 54,5 %, Ps. aeruginosa 9,1 %, Str. agalactiae 18,2 %, Enterococcus spp. 27,3 %). There was no significant difference in bacterial colonization with Str. Pyogenes, Str. Viridans, St. pneumoniae, C. albicans by severity of the disease.

A comparison of the vitamin D–sufficient and–insufficient groups showed that patients with sufficient serum 25 (OH) D_3 concentration were unlikely to have abnormal function of lungs. This group of children was associated with higher rates of FEV_1 (OR=2,971; 95% CI: 1,175-7,514; χ^2=5,440; p=0,020), and they had decreased risk to develop FEV1 deviation (OR=0,294; 95% CI: 0,095-0,903; χ^2=4.855; p=0,028).

The group of insufficient serum 25 (OH) D_3 concentration was associated with decreased FEV1 rate less than 64% (OR=3,400; 95% CI: 1,107-10,443; χ^2=4,855; p=0,028), comparatively to sufficient group (Table 2).

Table 2 - Odds ratio of FEV1 rate changing according to the sufficiency or insufficiency of serum 25 (OH) D_3 in children with CF

FEV_1	25 (OH) D3 level		χ^2	p value
	Insufficient (20 - 30 ng/ml)	Sufficient (30 – 50 ng/ml)		
	OR (95% CI)	OR (95% CI)		
80 % and >	0,337 (0,133-0,851)	2,971 (1,175-7,514)	5,440	0,020
65 – 79 %	1,296 (0,420-3,997)	0,771 (0,250-2,379)	0,205	0,652
64 % and <	3,400 (1,107-10,443)	0,294 (0,095-0,903)	4,855	0,028

We compared mean rates of serum 25 (OH) D_3 in culture-positive and culture-negative groups of children with CF. The mean serum 25 (OH) D_3 concentration in Pseudomonas-positive group was significantly lower than in Pseudomonas-negative group (26,22 ± 1,06 ng/ml and 30,51 ± 1,00 ng/ml respectively, p = 0,007). There was no significant difference between others bacteria (Table 3).

Children with vitamin D insufficiency were more likely to be colonized with P. aeruginosa. Group of children with decreased level of 25 (OH) D_3 was associated with *Ps. aeruginosa*-positive culture (OR=2,813; 95% CI: 1,048 – 7,548; χ^2=4,350; p=0,037), while patients with sufficient 25(OH) D_3 had lower risk (OR=0,356; 95% CI: 0,132 – 0,954; χ^2=4,350; p=0,037). There was no association among others bacteria.

Table 3 - Mean serum 25 (OH) D_3 concentration in culture-positive and culture-negative children with CF

Bacterial colonization	25 (OH) D_3 level			
	Positive culture		Negative culture	
	n	M ± m, ng/ml	n	M ± m, ng/ml
St.aureus	46	27,97 ± 1,09	38	30,21 ± 1,07
Ps. aeruginosa	30	26,22 ± 1,06*	54	30,51 ± 1,00
Str. pyogenes	28	28,03 ± 1,09	56	29,46 ± 1,03
Str. viridans	38	29,73 ± 1,25	46	28,36 ± 0,98
Str. agalactiae	16	28,81 ± 1,19	68	29,02 ± 0,92
St. pneumoniae	9	28,33 ± 1,70	75	29,06 ± 0,85
C. albicans	47	29,35 ± 1,03	37	28,50 ± 1,19
Enterococcus spp.	35	28,45 ± 1,22	49	29,36 ± 1,01

* p-value = 0,007

Assessment of relations between severity of CF and vitamin D status showed significant association of severe CF with insufficient serum 25 (OH) D_3 concentration (OR=10,197; 95% CI: 3,071-33,858 (χ^2=17,286; p=0,00003). Children with sufficient 25 (OH) D_3 were less predisposed to severe CF (OR=0,098; 95% CI: 0,029 – 0,326).

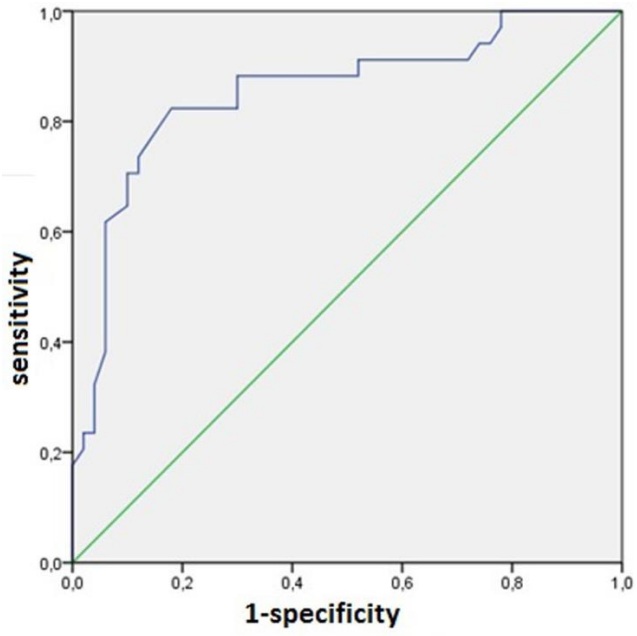

Figure 1 - ROC – curve: Serum (OH) D_3 concentration - severity of CF

For diagnostic test evaluation ROC curve analysis was made. Sensitivity of vitamin D status evaluation for prediction of the severity of CF was 70%, specificity 88%, AUC – 0,857;

95 % CI: 0,765 – 0,942 (p = 0,045) (Fig. 1). It was shown that 25 (OH) D_3 measurement is reliable marker for prediction of severity of the disease.

Conclusions

Measurement of serum vitamin D among children with cystic fibrosis showed that 58,3 % of subjects had insufficiency. Children who suffered from severe CF had significant lower serum 25 (OH) D_3 concentrations than patients with moderate and mild CF (24,23 ± 0,81 нг/мл, $p \leq 0,001$).

It was shown that children with suboptimal level of 25 (OH) D_3 had higher in 3,4 times risk of FEV_1 rate decreasing less than 64 % (OR=3.400; 95% CI: 1,107-10,443; χ^2=4,855; p=0,028), and significant association with *Ps. aeruginosa*-positive culture was detected (OR = 2,813; 95% CI: 1,048 – 7,548; χ^2=4,350; p=0,037).

Those subjects with sufficient 25 (OH) D_3 had strong association with higher rates of FEV_1 (OR=2,971; 95% CI: 1,175-7,514; χ^2=5.440; p=0,020) and risk of FEV_1 deviation was decreased (OR=0,294; 95% CI: 0,095-0,903; χ^2=4,855; p=0,028). Risk of *Ps. aeruginosa*-positive culture was also decreased (OR = 0,356; 95% CI: 0,132 – 0,954; χ^2=4,350; p=0,037).

Assessment of relations between severity of CF and vitamin D status showed that children with insufficient serum 25 (OH) D_3 concentration had more severe CF, than children with sufficient 25 (OH) D_3.

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