EDITORIAL

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VITAMIN D DEFICIENCY IN CHILDREN WITH CYSTIC FIBROSIS: IS THERE A LINK WITH THE MICROFLORA OF THE LOWER RESPIRATORY TRACT, THE FREQUENCY OF HOSPITALIZATIONS AND THE VOLUME OF ANTIBIOTIC THERAPY?

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Background. Cystic fibrosis (CF) – a hereditary disease which is characterized by a chronic infection and inflammation in airways and leads to the progressing of the lung damage and an early disability.

The aim of our study to evaluate the relationship between vitamin D deficiency and degree of the contamination of the lower airways (LA) by the main pathogens and requirement in intravenous (IV) antibacterial therapy and hospital admission duration.

Materials and methods. The study included 92 children with CF aged from 0 to 17 years. During the research (18 months) the serum 25(OH)D levels were evaluated trice. Vitamin D_3 titration dosage was made according the 25(OH)D level and data about treatment compliance collected. According to the register of patients the number of flares and days of antibacterial therapy for 3 periods was counted: during 1 year before inclusion in the study (2016), for 2017 (during treatment) and in 2018. Statistical analysis was carried out with Statistica 10.0 software.

Results. From 92 people, only 66 were compliant and in 38/66 the normal level of 25(OH)D was reached. At children with initially normal level of vitamin D the requirement in IV antibacterial therapy within the first year of observation decreased. In patients who had normal 25(OH)D serum level (>30 ng/ml) we observed decreased number of in-patient department admission and decreased frequency of gram-negative bacteria of LA detection.

Conclusions. The maintenance of normal blood vitamin D level was a perspective therapeutic strategy in CF patients which may reduce the frequency of a chronic infection and as a result, the requirements in hospital admission and IV antibacterial therapy.

Keywords: *cystic fibrosis*; vitamin D; 25(OH)D; antibacterial therapy; frequency of hospital admissions; infection.

ДЕФИЦИТ ВИТАМИНА D У ДЕТЕЙ С МУКОВИСЦИДОЗОМ: ЕСТЬ ЛИ СВЯЗЬ С МИКРОФЛОРОЙ НИЖНИХ ДЫХАТЕЛЬНЫХ ПУТЕЙ, ЧАСТОТОЙ ГОСПИТАЛИЗАЦИЙ И ПОТРЕБНОСТЬЮ В АНТИБАКТЕРИАЛЬНОЙ ТЕРАПИИ?

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Для цитирования: Пашкевич А.А., Начинкина Т.А., Ушатская О.А., и др. Дефицит витамина D у детей с муковисцидозом: есть ли связь с микрофлорой нижних дыхательных путей, частотой госпитализаций и потребностью в антибактериальной терапии? // Педиатр. – 2018. – Т. 9. – № 6. – С. 5–12. doi: 10.17816/PED965-12

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Актуальность. Муковисцидоз (МВ) – наследственное заболевание, характеризующееся хронической инфекцией и воспалением в дыхательных путях, что ведет к прогрессирующему повреждению легких и ранней инвалидизации.

Цель – изучить связь дефицита витамина D с выраженностью контаминации нижних дыхательных путей (НДП) основными патогенами, а также связь с потребностью в антибактериальной терапии и длительностью госпитализаций.

Материалы и методы. В исследование включены 92 ребенка с МВ в возрасте от 0 до 17 лет. В течение исследования (18 месяцев) всем пациентам определяли уровень 25(OH)D в крови три раза. По результатам проводили коррекцию дозировки препарата витамина D_3 в зависимости от уровня в крови и возраста, а также собирали данные о комплаентности. По данным реестра пациентов подсчитывали число обострений и дни антибактериальной терапии за три периода: один год до включения в исследование (2016), за 2017 г. (во время терапии) и за 2018 г. Статистическую обработку данных осуществляли с помощью пакета прикладных программ Statistica 10.0.

Результаты. Из 92 человек только 66 соблюдали режим терапии, нормальный уровень 25(OH)D был достигнут у 38/66. У детей с исходно нормальным уровнем витамина D в крови снизилась потребность во внутривенной антибактериальной терапии уже в течение первого года наблюдения. При поддержании концентрации 25(OH)D в крови более 30 нг/мл доказано снижение числа госпитализаций и частоты высевов грамотрицательной микрофлоры НДП.

Выводы. Поддержание нормального уровня витамина D в крови оказалось перспективной терапевтической стратегией у пациентов с МВ, при этом уменьшилась частота хронической инфекции и, как следствие, потребность в госпитализациях с проведением антибактериальной терапии.

Ключевые слова: муковисцидоз; *cystic fibrosis*; витамин D; 25(OH)D; антибактериальная терапия; частота госпитализаций; инфекция.

BACKGROUND

Cystic fibrosis (CF) is a genetic disease with a severe course and poor prognosis. Respiratory disease and impaired bronchopulmonary are the primary causes of mortality and death, but other systems may become affected [2, 22]. Treatment and disease control depend on prevention and early detection of lung lesions antibacterial, anti-inflammatory, and mucolytic agents, kinesiotherapy, and maintenance of normal nutrition. The search for novel treatments and drugs to improve the quality of life of CF patients is ongoing.

Vitamin D activity may be involved in some chronic diseases affected by changes in the immune system [4, 10, 11]. Serum 25(OH)D concentrations are above the normal range in CF, and respiratory function indexes are higher when 25(OH)D levels are normal than they are deficient [6, 17]. Vitamin D

has anti-inflammatory activity [14, 21], induces the production of antimicrobial peptides [7], and affects bronchial muscle activity [12]. Bronchopulmonary exacerbations are less frequent in CF patients with normal serum vitamin D and rarely require treatment with intravenous antibiotics [9, 15]. The benefits of including vitamin D supplementation in the routine treatment of CF patients are not yet supported and require additional study [20]. This study investigated the effects of serum vitamin D levels on the need of antibiotic treatment, hospitalization rate, and the composition of the microflora of the lower respiratory airway (LRA) in pediatric CF patients in St. Petersburg, Russia.

MATERIAL AND METHODS

Patients and study procedures

Ninety-two pediatric CF patients, 49 boys and 43 girls, from 0 to 17 years of age were prospectively enrolled at the City Childrens' Hospital of St. Olga in St. Petersburg, Russia. The diagnosis of CF the followed the 2014 European Cystic Fibrosis Society criteria [18]. Thirty-three patients were younger than 3, 21 were 3 to 6, 24 were 6 to 12, and 14 were 12 to 18 years of age. Fasting serum 25(OH)D was assayed with an Architect i1000 autoanalyzer (Abbott, USA) before the start of vitamin D_3 treatment. The reagents and the control and calibration materials were supplied by the device manufacturer. The range of measurement was 4 to 160 ng/ml The equipment and reagents were approved by the Federal Service on Surveillance in Health Care and Social Development of the Russian Federation for diagnostic use in medical practice. Serum 25(OH)D was assayed between January and March 2017, October and December 2017, and March and April 2018. At those times of the year in northwest Russia the available sunlight is not sufficient to promote significant vitamin D synthesis in the skin [3]. No patients were taking vitamin D_3 supplements on a regular basis at enrollment; preparations were prescribed at currently recommended dosages [1, 19]. Water soluble formulations were recommended, but the choice was made by the patient. The objective was adherence to the regimen at the recommended daily dose in international units. Vitamin D_3 therapy continued throughout 2017 and the first 6 months of 2018. If the serum 25(OH)D was <30 ng/ml 6 months after starting vitamin D_3 supplementation, then the dose was adjusted. Patients and/or their legal guardians were asked about the regularity of vitamin D_3 dosing when they returned for the second and third 25(OH)D assay. Adherence to treatment was <80% in 26 patients, and they were excluded from the analysis. The numbers of exacerbations and days of antibacterial therapy were retrieved from the patients' hospital medical records, archived clinic records, and outpatient medical records. Exacerbations were diagnosed and described based on generally accepted criteria [5, 8, 16]. Bacteriological evaluation included microflora typical of CF, and Pseudomonas aeruginosa infections were considered chronic or intermittent as described by Lee et al. [13]. The number of days of antibacterial therapy, duration of hospitalization, were recorded for each infection. Changes of the composition of the LRA microbiota that accompanied regular intake of vitamin D_3 were evaluated annually from 2016 to 2018. The severity, form of disease, and ages of patients with normal and deficient serum 25(OH)D concentrations were comparable.

Statistical analysis

Statistical analysis was performed with Statistica 10.0. The results were reported as medians and interquartile range. Nonparametric methods, the Mann–Whitney and the Kruskal–Wallis tests, were used to compare the values of two or more independent quantitative variables. The chi-square and Fisher's exact tests were used to compare the values of independent categorical variables. The Wilcoxon and Friedman tests were used to compare the values of two or more dependent quantitative variables. The McNemar test was used to compare the values of dependent categorical variables, Correlation analysis was performed by the Spearman method. P-values < 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

The effects of vitamin D_3 supplementation on serum 25(OH)D and the use of intravenous antibiotics are shown in Table 1. The initial serum 25(OH)D was normal in 18 of the 92 enrolled patients (19%) and < 30 ng/ml in 74 (81%). In patients with normal baseline serum 25(OH)D, the number of days of intravenous antibacterial therapy significantly decreased from 14.5 in 2016 to 5.5 in 2017. In patients with reduced serum 25(OH)D at baseline, the need for intravenous antibiotic therapy did not change, 14 days in both 2016 and 2017. The number of days of intravenous antibacterial therapy and the vitamin D level were negatively correlated ($r = –0.226$, $p = 0.03$). Normal serum 25(OH)D levels were achieved by 38 of 66 treatment-adherent patients within 1 year of treatment. Normalization was accompanied by a decrease in the number of days of intravenous antibiotic therapy during follow-up. There was no reduction in the number of days of intravenous antibiotics in the 28 compliant patients who did not achieve

Table 1 / Таблица 1

Dynamics of days of intravenous anti-bacterial therapy in compliant patients, depending on the achievement of normal levels of vitamin D in the blood

Динамика дней внутривенной антибактериальной терапии у комплаентных пациентов в зависимости от достижения нормального уровня витамина D в крови

Level 25(OH)D, ng/ml / Уровень 25(OH)D, нг/мл	2017 y. (days) / 2017 г. (дни)	2018 y. (days) / 2018 г. (дни)	*p*
> 30 (*n* = 38)	14.0 (0.0–20.0)	0.0 (0.0–13.0)	0.0005
< 30 (*n* = 28)	14.0 (0.0–18.5)	6.5 (0.0–14.0)	0.49

Table 2 / Таблица 2

Dynamics of days of intravenous antibiotic therapy depending on normal serum vitamin D levels throughout the study

Динамика дней внутривенной антибактериальной терапии в зависимости от нормального уровня витамина D в сыворотке крови на протяжении всего исследования

Level 25(OH)D, ng/ml / Уровень 25(OH)D, нг/мл	2016 y. (days) / 2016 г. (дни)	2017 y. (days) / 2017 г. (дни)	2018 y. (days) / 2018 г. (дни)
> 30 (*n* = 12)	14.0 (0.0–15.5)	0.0 (0.0–14.0)	0.0 (0.0–0.0)
< 30 (*n* = 43)	14.0 (13–27.0)	14.0 (0.0–21.0)	14.0 (0.0–15.0)
p	0.21	0.01	0.04

Table 3 / Таблица 3

Dynamics of the number of hospitalization in complementary patients, depending on the achievement of normal levels of vitamin D in the blood

Динамика числа госпитализаций у комплаентных пациентов в зависимости от достижения нормального уровня витамина D в крови

Level 25(OH)D, ng/ml / Уровень 25(OH)D, нг/мл	2017 y. (number) / 2017 г. (количество)	2018 y. (number) / 2018 г. (количество)	*p*
> 30 (*n* = 38)	1.0 (0.0–1.0)	0.0 (0.0–1.0)	0.002
< 30 (*n* = 21)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.14

normal serum 25(OH)D levels. As shown in Table 2, 12 patients with 25(OH)D levels > 30 ng/ml had no need for intravenous antibacterial therapy during the 3 years of follow-up. Patients with low levels continued to receive intravenous antibiotics annually with the same frequency. In 2017, which was the first year of follow-up, children with normal serum 25(OH)D were prescribed oral antibiotics despite the lack of need for intravenous antibiotics. Successful treatment with oral drugs suggests that the severity of the bronchopulmonary exacerbations had been reduced by vitamin D_3 supplementation. Those patients required neither oral nor intravenous antibiotic treatment during year 2 of follow-up. Maintaining normal serum 25(OH)D levels not only reduced the need for intravenous antibiotics, but was also associated with fewer annual hospitalizations. The number of hospitalizations did not decrease in patients with a low serum 25(OH)D (Table 3).

Pathogenic microflora were rarely detected in the LRA of children with chronic and intermittent exacerbations and normal serum 25(OH)D levels (Table 4). The microbial landscape of the LRA in patients with low levels was significantly differ-

Table 4 / Таблица 4

Dynamics of infection depending on normal serum vitamin D levels throughout the study
Динамика инфекции в зависимости от нормального уровня витамина D в сыворотке крови на протяжении всего исследования

Infection / Инфекция	Level 25(OH)D, ng/ml / Уровень 25(OH)D, нг/мл		*p*
	< 30 (*n* = 43)	> 30 (*n* = 12)	
2016			
No / Нет	4 (9.3)	3 (25.0)	0.15
PA chron.	8 (18.6)	1 (8.3)	0.39
PA inter.	9 (20.9)	0 (0.0)	0.08
MSSA	26 (60.5)	8 (66.7)	0.69
MRSA	7 (16.3)	0 (0.0)	0.13
BCC	1 (2.3)	0 (0.0)	0.59
AX	0 (0.0)	0 (0.0)	–
Other Gr «–»	5 (11.6)	3 (25.0)	0.24
2017			
No / Нет	4 (9.3)	1 (8.3)	0.92
PA chron.	9 (20.9)	0 (0.0)	0.16
PA inter.	7 (16.3)	2 (16.7)	0.05
MSSA	26 (60.5)	8 (66.7)	0.69
MRSA	6 (13.9)	1 (8.3)	0.07
BCC	1 (2.3)	1 (8.3)	0.14
AX	2 (4.6)	2 (16.7)	0.02
Other Gr «–»	14 (32.5)	3 (25.0)	0.62
2018			
No / Нет	6 (13.9)	0 (0.0)	0.17
PA chron.	6 (13.9)	1 (8.3)	0.61
PA inter.	6 (13.9)	2 (16.7)	0.81
MSSA	26 (60.5)	8 (66.7)	0.69
MRSA	2 (4.6)	0 (0.0)	0.45
BCC	2 (4.65)	0 (0.0)	0.45
AX	3 (6.9)	0 (0.0)	0.35
Other Gr «–»	8 (18.6)	6 (50.0)	0.03
p	> 0.05	> 0.05	

Note / Примечание. No / Нет (no chronic or intermittent infection / нет хронической или интермиттирующей инфекции). PA chron. (chronic *Pseudomonas aeruginosa* / хроническая *Pseudomonas aeruginosa*). PA inter. (intermittent *Pseudomonas aeruginosa* / интермиттирующая *Pseudomonas aeruginosa*). MSSA (chronic methicillin-sensitive *Staphylococcus aureus* / хронический метициллин-чувствительный *Staphylococcus aureus*). MRSA (chronic methicillin-resistant *Staphylococcus aureus* / хронический метициллин-резистентный *Staphylococcus aureus*). BCC (chronic *Burkholderia cepacia comlex* / хроническая *Burkholderia cepacia comlex*). AX (chronic *Achromobacter xylosoxidans* / хроническая *Achromobacter xylosoxidans*). Other Gr «–» (any other chronic or intermittent gram «–» flora, except for the above / любая другая хроническая или интермиттирующая грамотрицательная флора, кроме вышеуказанной).

ent. In 2017 there was a tendency toward decreased detection of pathogenic microorganisms in patients with normal serum 25(OH)D but that was not observed in patients with low serum 25(OH)D. With time, pathogenic microflora appear in the LRA microbiota of all CF patients, which inevitably leads to an increase in the amount of therapy and a worsening of the course of the disease. The search for novel treatments is ongoing, and the routine addition of vitamin D supplementation may prove to be one of them. Maintenance of a stable serum 25(OH)D concentration of > 30 ng/ml, decreased the number of days of intravenous antibiotics, the frequency of hospitalization, and a decrease in the frequency of detection of pathogenic microflora in the LRA.

CONCLUSION

Normalization and maintenance of a serum vitamin D concentration of > 30 ng/ml reduced the number of days of intravenous antibacterial therapy, the number of days spent in the hospital, the frequency of hospitalization, and the infectious load. Despite adequate doses of vitamin D_3 and patient adherence to treatment, it was not possible to normalize serum 25(OH)D levels and stabilize the clinical situation in all patients.

The search for treatments that alleviate inflammation in the lungs in CF patients continues. Adjustment of vitamin D levels may prove to be an effective addition to current CF therapies. A decrease in the number of infectious events would reduce the severity of damage to the pulmonary parenchyma, risk of progression to respiratory failure, and improve patient quality of life.

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