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Vitamin D deficiency in children with recurrent respiratory infections, with or without immunoglobulin deficiency

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ABSTRACT

Purpose: The objective of this study was to evaluate thevitamin D concentration in patients with recurrent respiratory infections with or without immunoglobulin G, A or M (IgG, IgA, IgM) deficiency, and to find a correlation between the vitamin D concentration and the response to hepatitis B vaccination.
Materials and method: The study involved 730 patients with recurrent respiratory infections. The concentration of 25-hydroxyvitamin D (25(OH)D), immunoglobulins G, A and M, anti-HBs was determined.
Results: The tests showed that 11% of patients presented IgG levels below the age related reference values. Children with reduced IgG concentration were also found to have significantly lower vitamin D concentrations in comparison to children with normal IgG. Vitamin D deficiency was observed in schoolchildren between 7 and 18 years of age. No correlation was found between 25(OH)D concentration and Hbs antibody levels.
Conclusions: An investigation of a large group of patients who have recurrent infection found patients with IgG deficiency to whom special proceeding have to be performed: 1. Significantly lower vitamin D concentration observed in the group of children with IgG deficiency implicated in long-lasting monitoring of vitamin D level require adding to the practice guidelines for Central Europe 2013. 2. Intervention treatment with suitable doses of vitamin D to clarified metabolism of vitamin D has to be plan for children with IgG deficiency and significant lower vitamin D concentration.

1. Introduction

The problem of vitamin D deficiency has been known since the 19th-century industrial revolution. In 1822 Jędrzej Śniadecki noticed that rickets symptoms in children could be the result of insufficient sun exposure. Nowadays rickets is a rare disorder in children and the presence of the vitamin D receptor (VDR) outside the skeletal system cells confirms its role in the patho-mechanism of many diseases. This mainly relates to the circulatory and respiratory systems, connective tissue and the development of autoimmune and neoplastic diseases [1]. As determined, a higher vitamin D concentration is required outside the skeletal system to maintain the correct metabolism [2].

The optimum 25(OH)D concentration in Poland was assumed to be between 30 and 50 ng/ml. It is estimated that a vitamin D deficiency (vitamin D concentration lower than 30 ng/ml) is widespread globally and relates to about 1 billion people. These are usually elderly people (40–100% of the population) and children [1,3].

Epidemiological studies conducted in Poland show that only 3-month-old infants have a vitamin D3 concentration of more than 20 ng/ml. Vitamin D deficit, in turn, defined as a concentration below 20 ng/ml, relates to 20% of infants at 12 months, and 85% of 12–19-year-olds [4].

Despite numerous experimental studies and clinical observations, only limited information on the role of vitamin D in children with recurrent respiratory infections and immune system disorders can be found.

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The available data on the correlation between vitamin D deficiency and presence of a higher frequency of acute respiratory infections, plus tuberculosis, is ambiguous [5–15].

It was demonstrated that in the group of patients with immune deficiencies, introducing vitamin D3 supplementation in doses of 4000 IU/day caused a significant reduction in infection symptoms, the number of pathogenic bacteria in nasal swabs, and antibiotic consumption [16]. It was also determined that in children with vitamin D deficiencies, introducing vitamin-D-enriched milk resulted in a significant reduction in the frequency of acute respiratory infections over the 3-month observation period [17].

The supplementation of young adults with vitamin D in an accumulated dose of 100,000 IU per month, in comparison to the placebo group, did not result in any reduction of the frequency of respiratory infections. However, this was a population without significant vitamin D deficiencies (the average concentration of 25 (OH)D was 29 ng/ml) [11].

In addition, a correlation between the vitamin D receptor (VDR) gene polymorphism and an increased frequency of respiratory infections was found. The VDR Fok-I ff genotype increases the risk of acute respiratory infections (RSV bronchiolitis and respiratory infections caused by the influenza virus [18–21]).

Laboratory studies confirm the influence of vitamin D on innate and adaptive immunity. Vitamin D's antiviral and antibacterial effects arise mainly from its interaction with macrophages and monocytes. It increases the production of cathelicidins and defensins, which exhibit direct antibacterial and antiviral activity [22–24], affect the chemotaxic and phagocytic capabilities of monocytes and macrophages [25,26] and increase the monocyte to macrophage differentiation [27].

In addition, studies relating to the influence of vitamin D on vaccination response [28–34] generate much controversy, suggesting a favourable influence [29,30,34], no influence [28,32,], or adverse influence [31] of vitamin D on the production of vaccination antibodies.

With the above in mind, the objective of this study was to evaluate the vitamin D concentration in patients with recurrent respiratory infections, with or without immunoglobulin G, A or M (IgG, IgA, IgM) deficiency, and to find a correlation between the vitamin D concentration and response to hepatitis B vaccination.

2. Materials and method

2.1. The study population included 730 patients (435 boys and 295 girls) aged from 4 months to 18 years of age referred to the Department of Immunology of the Children's Memorial Health Institute between October 2011 and April 2013 with suspected primary immunodeficiency (PID) and with recurrent respiratory infections. The inclusion criteria for the study included more than 8 respiratory infections per year, of a mild course requiring no hospitalisation. Vitamin D supplementation was not provided in this group of patients except the infants from 0 to 2 age group. The criteria for exclusion from the study were acute infection, immunosuppressive and steroids treatment, and vitamin D3 suplementation in children over 2 years of age. Patients were divided into 5 age groups (Fig. 1) and, depending on IgG concentration (correct, reduced or elevated) using age norms [35], 3 groups were distinguished.

2.2. The total serum concentration of 25(OH)D (25(OH)D_2 and 25(OH)D_3) was determined using the automatic method based on immunochemiluminescence, with an LIASON test (DiaSorin, Sallugia, Italy, controlled and certified by the International Vitamin D Proficiency a Testing Program (DEQAS), coefficient of variation – CV $\leq$ 4,0 ng/ml). Vitamin D deficiency was confirmed at 25(OH)D $<$20 ng/ml, suboptimal concentration at 20–30 ng/ml, optimal concentration at 30–50 ng/ml, and high concentration at 50–100 ng/ml, toxic: $>$200 ng/ml [36].

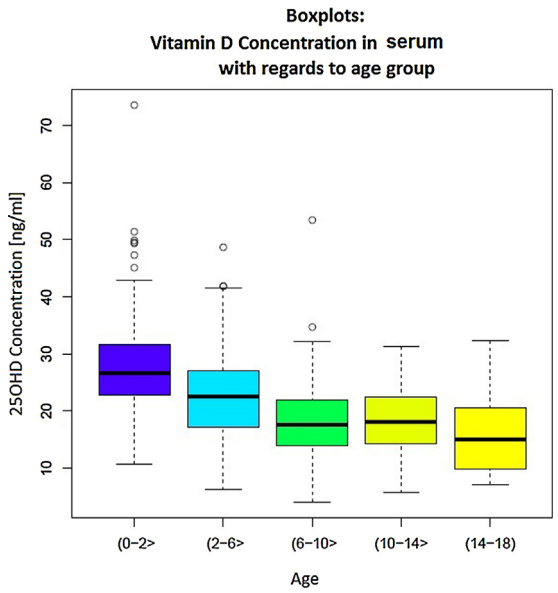

Fig. 1. Vitamin D concentration in serum with regards to age group.

In 645 patients, IgG, IgA and IgM were determined by nephelometry on a BN ProsPec device by Siemens.

In 604 patients vaccinated in the infancy period with 3 doses of hepatitis B vaccine the concentration of anti-HBs was measured in an immunoenzymatic assay conducted on average 5 years and 2 months after vaccination.

Ethical approval for the study was obtained from the Bioethics Committee at the Children's Memorial Health Institute (Nr 20/KBE/2017).

2.3. To determine the statistically significant differences in the 25(OH)D serum concentration in the 3 groups of patients with a correct, reduced and elevated concentration of IgG, Tukey's HSD test was performed. The Shapiro-Wilk test was used to determine whether the 25(OH)D serum concentration values in individual immunoglobulin concentration groups (correct, high, low) met normal distribution assumptions for the sources of the analysed samples. The F-test was used to compare the homogeneity of 25 (OH)D results in various IgG result groups.

To determine the existence of a correlation between the serum concentration of 25(OH)D and the concentration of anti-HBs, the Pearson correlation analysis was used.

3. Results

3.1. In the studied group of 730 patients, the average serum concentration of 25(OH)D was 21.96 ng/ml (median 21.5 ng/ml). There was a remarkably high dispersion of values – from 4.1 ng/ml to 73.5 ng/ml. Vitamin D deficiency, defined as a serum concentration of 25(OH)D below 20 ng/ml, was found in 315 children (43.1%), whereas a suboptimal concentration was found in 627 subjects (85.9%). Optimal vitamin D serum concentrations (between 30 and 50 ng/ml) were found only in 100 children (13.7%). Three patients had high, above-optimum, vitamin D concentrations (0.4%), and no child had a toxic concentration (Fig. 1).

3.2. The IgG concentration was analysed in 645 patients. In 68 subjects (about 11%) an IgG level below the norm for age was found, in 85% (551 patients) the IgG concentration was normal, and 4% (26 patients) had an IgG level below the norm (Fig. 2).