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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].

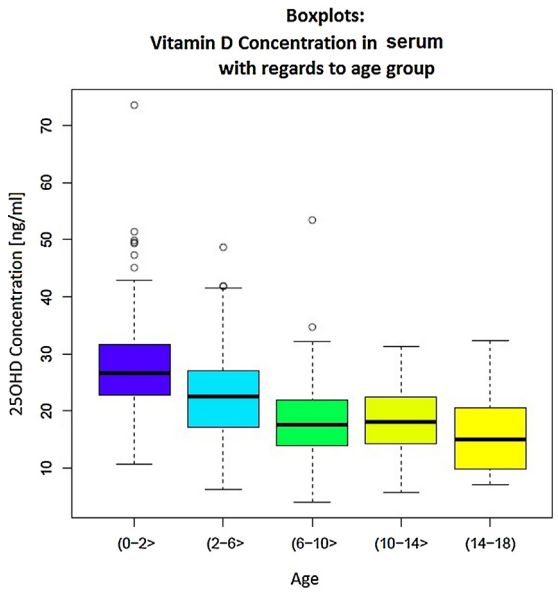

Fig. 1. Vitamin D concentration in serum with regards to age group.

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).

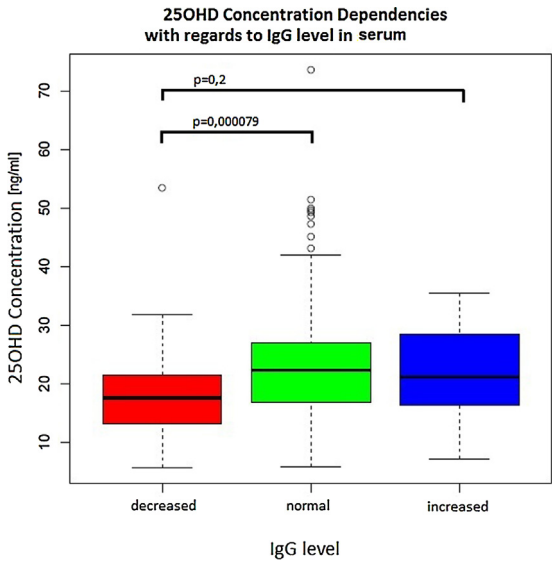

Fig. 2. 25OHD concentration dependencies with regards to IgG level in serum.

3.3. An assessment of the 25(OH)D serum concentration, depending on the IgG level, demonstrated that patients with reduced IgG had statistically-significant lower vitamin D concentrations than children with normal concentrations of IgG (average serum concentration 25(OH)D 18.04 ng/ml vs 22.51 ng/ml; p = 0.000079) (Fig. 2).

3.4. The group of 68 children with an IgG concentration below the age norm (less than 2 standard deviations) were mostly children aged between 7 and 18. There were twice as many boys as girls in that group. It should be stressed that a reduced IgG concentration was found in 26% of children aged 7 to 10. The average 25(OH)D serum concentration in boys was lower than in girls (16.5 ng/ml vs 21.29 ng/ml) (Table 1).

Isolated hypogammaglobulinemia G was found in the majority of the children (72%). If IgG deficiency is accompanied by reduced IgA concentration, the average 25(OH)D concentration was suboptimal (24.27 ng/ml), and in children with reduced IgG and IgM a deficit of 25(OH)D was found (8.03 ng/ml) (Table 2).

3.5. The study demonstrated that vitamin D serum concentrations differed depending on the season during which the tests were conducted, and the age of the children. The highest average serum concentration, 25(OH)D, 26.1 ng/ml, was found in the summer, and the lowest, 19.26 ng/ml, in the winter. In spring and autumn the average serum concentrations of 25(OH)D were similar and amounted to over 22 ng/ml (Table 3). The resulting serum concentrations of 25(OH)D depending on age are shown in Table 1 and Fig. 1. The highest average concentration of 25(OH), 27.98 ng/ml was found in children aged 0–2, and the lowest, 16.17 ng/ml, in teenagers from 15 to 18 years of age.

3.6. A Pearson correlation analysis between the 25(OH)D concentration and the concentration of anti-HBs did not show any correlation (r = 0.1604; p-value = 1e-04 < 0.05); also when outliers for vitamin D concentrations were discarded (r = 0.1676; p-value = 8e-05 < 0.05).

4. Discussion

In the study group of 730 children with recurrent respiratory infections and mild symptoms, an IgG deficiency was found in only about 11%. This deficiency was mainly found in school-age children and in twice as many boys as girls. Such patients did not fulfil the inclusion criteria to the Therapeutic Health Programme Treatment of Primary Immuno-deficiencies in Children – a substitution treatment with intravenous or subcutaneous gamma globulin preparations [37].

Our studies demonstrated that patients with IgG concentrations below the age norms also had vitamin D3 deficiencies. It was also found that patients with normal or above-average IgG had a suboptimal, i.e. 20–30 ng/ml, average vitamin D3 concentration.

Currently there are no unambiguous studies on this issue that could fully explain the connection between the low concentration of vitamin D3 and IgG. There are only a few studies in the literature investigating the correlation between vitamin D and IgG concentrations [38,39].

It is worth mentioning that for patients with cystic fibrosis and severe symptoms of pneumonia, who had a lower 25(OH)D concentration and a higher total IgG concentration, as well as a 7-day vitamin D supplementation, this caused a reduction in IgG concentration and improved functioning of the lungs [39]. The reduction in the IgG concentration was probably caused primarily by the inhibitory effect of vitamin D on the mobilised B lymphocytes. Another study, conducted among healthy elderly people (1470 subjects), aged over 60, showed that in the summer the IgG concentration rises along with the 25(OH)D concentration [40].

It is thought that vitamin D, by acting on the mobilised B lymphocyte, causes, inter alia, a reduction in the concentration of excessively produced immunoglobulins, which happens in autoimmune diseases [38]. An inhibitory effect of 1.25(OH)2D on E immunoglobulin production by B lymphocytes is also observed [41]. In addition, calcitriol can inhibit the function of B lymphocyes by CD4+ lymphocytes [42] and the production of proinflammatory cytokines by monocytes and monophages.

This can also act directly on the VDR in B lymphocytes, inducing the expression of protein genes that inhibit the proliferation of activated B lymphocytes, plasmacytic differentiation, immunoglobulin secretion and class switching, and inducing the apoptosis of activated B cells [43]. In-vitro research showed that vitamin D acted as an inhibitor of antibody synthesis.

The influence of vitamin D on adaptive immunity is also exerted through T lymphocytes. By acting on Th1 lymphocytes, it causes a reduction in the production of proinflammatory cytokines (IL-2L IFNγ) and by acting on Th2 lymphocytes, increases the production of such cytokines as IL4, IL5, IL13 and IL10. Moreover, through Th17 lymphocytes, vitamin D inhibits inflammatory and auto-immunisation processes and, through regulatory T lymphocytes, inhibits the production of IL10 and TGF.

Table 1
Patients with reduced IgG concentration by age, gender and 25(OH)D serum concentration.

Age	Number	Average 25(OH)D concentration[ng/ml]	Number of boys:girls	Average 25(OH)D concentration [ng/ml] boys:girls
0–2	2/116 (1.7%)	25.85	1:1	24.4:27.3
3–6	20/334 (6%)	17.44	15:5	16.97:18.86
7–10	33/127 (26%)	18.77	20:13	17.02:21.48
11–14	9/43 (20.9%)	15.92	7:2	14.66:20.35
15–18	4/20 (20%)	15.98	3:1	12.36:26.8
Total	68/645 (10.5%)	18.04	46:22	16.5:21.29

Table 2
IgG deficiency – the number of patients and 25(OH)D serum concentration depending on the associated IgA and IgM deficiencies.

Ig	Number of patients	Average 25(OH)D concentrations [ng/ml]
↓IgG	49 (72%)	18.1
↓IgG + ↓IgA	7 (10.3%)	24.27
↓IgG + ↓IgA + ↓IgM	5 (7.4%)	13.35
↓IgG + ↓IgM	6 (8.8%)	8.03
↓IgG + ↓IgM	1 (1.5%)	17.2
Total	68	18.04

Table 3
25(OH)D serum concentration by season.

Season	Number of patients	Range of 25(OH)D concentration [ng/ml]	Average 25(OH)D concentration [ng/ml]	Median 25(OH)D concentration [ng/ml]	SD [ng/ml]
Spring	147	5.7–53.4	22.66	20.9	9.35
Summer	90	8.8–73.5	26.1	25	7.86
Autumn	273	5.85–49.5	22.38	22.5	7.35
Winter	220	4.1–49.9	19.26	18.55	8.02
Total	730	4.1–73.5	21.96	21.5	8.33

It is possible that vitamin D not only causes a reduction in immunoglobulins during the activation of the immune system, but also stimulates resting B lymphocytes directly or indirectly through dendritic cells and T lymphocytes to produce immunoglobulins. The literature data show that patients with innate immunodeficiencies such as the common variable immunodeficiency (CVID) and ataxia telangiectasia are often found to have vitamin D deficiencies [44]. Vitamin D deficiencies in CVID patients correlate with longer respiratory infections and the necessity for hospital treatment [45]. Vitamin D deficiencies are observed not only in people with enteropathy and secondary vitamin D absorption disorders, but also in those without enteropathy [46,47]. This can be related to VDR gene polymorphism. A correlation was found between the presence of an Apa I polymorphism (locations in the VDR gene recognised by the Apa I restriction enzyme) with B-cell lymphopenia and CD8 + CD57 + lymphocytosis in CVID patients [42].

Work on the effects of vitamin D on the outcome of the stem-cell-transplant procedure is worth noting. It was determined that children with higher vitamin D concentrations were more susceptible to the acute form of the disease, GVHD, had lower IgG concentrations, and required substitution with immunoglobulin preparations [48,49].

Our studies showed that vitamin D3 supplementation was needed in patients with reduced immunoglobulin G levels, and also in the case of associated reduced IgA and IgM concentrations. In the group of patients with reduced concentrations in two immunoglobulin classes, IgG and IgM, the vitamin D deficit was higher than in the group with combined IgG and IgA deficiencies. However, these observations applied to small groups of patients.

The literature data on the necessity of administering vitamin D to patients with recurrent respiratory infections is inconclusive. A systematic review of randomised intervention studies did not show that vitamin D supplementation had any effect on the prevention of acute respiratory infections in healthy children (RR 0.79, 95% (confidence interval (CI) 0.55–1.13) or on the number of hospitalisations due to respiratory infections (RR 1.18, 95% (CI 0.72–1.26)). In children diagnosed with asthma receiving vitamin D supplementation, the exacerbation frequency was reduced by 74% (RR 0.26, 95% (CI 0.11–0.59) [50].

A review of observational studies and a meta-analysis conducted on patients with a life-threatening condition showed the presence of an increased risk of infection (risk ratio (RR) 1.49, 95% (CI 1.12–1.99), P = 0.007), sepsis (RR 1.46, 95% (CI 1.27–1.68), $p < 0.001$) and death within 30 days (RR 1.42, 95% (CI 1.00–2.02), P = 0.05) in patients with 25(OH)D concentrations below 20 ng/dl. [51]. Assessment of 25(OH)D levels in patient with recurrent acute respiratory infections is recommended now by practice guidelines for Central Europe 2013 for some group of chronic diseases, but not for immunodeficiency condition [36]. In group of IgG deficiency children implicated in long-lasting monitoring of vitamin D level require adding to this practice guideline [36].

Additionally, the effect of vitamin D on the production of vaccine antibodies is an open issue. Our tests showed that there was no correlation between the vitamin D concentration and the concentration of antibodies following a hepatitis B vaccination. It should be stressed, however, that they were conducted at various periods after the vaccination. Research on animal models shows that calcitriol induces the migration of dendritic cells from the location of the vaccination to the local lymph nodes and stimulates antigen-specific T and B cells, thus increasing the production of vaccine antibodies [52,53]. However, prospective studies on healthy volunteers did not show any effect of vitamin D on the humoral response after vaccinations [28,54]. An elevated concentration of specific antibodies was found among the subjects immunised in winter in the group of pre-school children vaccinated against rubella in their first year of life [55].

An analysis of vitamin D concentrations in our patients referred to the Department of Immunology due to recurrent respiratory infections demonstrated that the lowest vitamin D concentrations were present in winter and the highest in summer, as observed by others [3]. Even in summer the average concentration of 25(OH)D did not reach optimal values. It should be pointed out that these values were similar for spring and autumn.

Our study and other authors confirmed that high vitamin D level in the first two years of life was the result of regular supplementation of vitamin D in this age group and a diet rich in vitamin D [56]. The deficiencies found in school-age children, particularly teenagers (aged 14–18), where only some individuals had optimal 25(OH)D concentrations, (i.e. 30–50 ng/ml) can be caused by their lifestyle. Large numbers of hours spent in front of a computer screen, avoiding the sun at midday, and using sun creams can result in significant deficiencies, even in summer. Similarly, children with recurrent respiratory infections are more susceptible to vitamin D deficiencies due to staying indoors, unlike their healthier peers.

There are a number of reports showing that vitamin D causes reduced immunoglobulin concentrations [38,39,43], but our

studies demonstrated that IgG deficiency does not result from the synthesis-inhibiting effect of vitamin D. In the group of children with IgG deficiencies, vitamin D concentrations were significantly lower than in other patients without IgG deficiencies, something that was also observed in patients with primary and secondary immunodeficiencies [44]. No correlation was found between the concentration of hepatitis B antibodies and vitamin D in comparison with other investigations [34].

5. Conclusions

An investigation of a large group of patients who have recurrent infection founded 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.

An analysis of the influence of vitamin D on vaccination response following hepatitis B vaccination did not confirm the hypothesis suggesting a favourable influence of vitamin D on the production of vaccination antibodies.

Conflict of interests

The authors declare no conflict of interests.

Financial disclosure

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