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Research Article

Vitamin D Deficiency and the Severity of COVID-19 Infection in Children -

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ABSTRACT

Background: Several studies have observed a strong correlation between vitamin D levels and cytokine storm seen in patients with severe forms of COVID-19. An optimal level of vitamin D in the body could protect patients against serious complications of infection. We propose through this case-control study, to determine the vitamin D status of children hospitalized for COVID-19 infection and to compare the vitamin D status of children with mild to moderate form to those who presented with a severe form.

Methods: Our study is a cross-sectional, case-control, prospective, descriptive, analytical and unicentric study. The inclusion of healthy infants was done chronologically during the year. The study took place from September 01, 2020 to September 01, 2021. SPSS 22 software was used for the statistical analysis. First, we carried out a descriptive analysis of the study population. In a second step, a univariate analysis. The significance level of the statistical tests and the simple and multiple logistic regression is $p < 0.05$.

Results: The analysis concerns 55 children whose COVID-19 infection was proven by carrying out a PCR, the average age was 4.5 years divided into 2 groups: those hospitalized for a mild to moderate form (43 cases) and those hospitalized for a severe form (12 cases). The mean level of 25 OHD in the series was 13.4 ± 2.2 ng/ml. Patients with a severe form had lower vitamin D levels than those hospitalized for a mild to moderate form (8.8 ± 0.5 ng/ml vs. 18 ± 4 ng/ml) ($p = 0.0001$). Children with severe form (12/12) had vitamin D deficiency (25 OHD level below 10 ng/ml) while patients with mild to moderate form (43/43) had vitamin D deficiency. D (25 OHD level less than 20 ng/ml), no case of deficiency was observed in this group.

Conclusion: An optimal level of vitamin D in the body could protect patients against serious complications of COVID-19 infection.

Keywords: COVID-19; Vitamin D; Child; Deficiency; Algeria

INTRODUCTION

The field of vitamin D research has grown exponentially in recent years due to a better understanding of its biological importance. Vitamin D, via its active metabolites, regulates more than 200 genes, including genes responsible for, cell differentiation and apoptosis. The discovery of the expression of vitamin D nuclear receptors and vitamin D metabolic enzymes in immune cells provides scientific justification for the potential role of vitamin D in maintaining immune homeostasis and in preventing development of autoimmune processes. The relatively high prevalence of low vitamin D status has been reported globally in recent decades in a wide range of population groups, including in low latitude areas (despite abundant sunlight). Vitamin D appears to inhibit lung inflammatory responses while enhancing innate defense mechanisms against respiratory pathogens. Population-based observational studies show positive associations between circulating 25OHD concentration and lung function and independent associations between low serum 25-hydroxyvitamin D concentration and susceptibility to respiratory tract infections [1].

We propose through this case-control study, to determine the vitamin D status of children hospitalized for COVID-19 infection and to compare the vitamin D status of children with mild to moderate form to those who presented with a severe form. The study took place from September 01, 2020 to September 01, 2021.

METHODS

Our study is a cross-sectional, case-control, prospective, descriptive, analytical and unicentric study. The inclusion of healthy infants was done chronologically during the year. The duration of the study was 1 year, from September 01, 2020 to September 01, 2021 after obtaining the written and signed consent of the parents, all regulatory approvals were obtained (Ministry of Health, Ministry of Higher Education and Scientific Research and the National Statistics Office).

We included the children hospitalized for a COVID-19 infection proven by performing a PCR. The patients were divided into 2 groups: those hospitalized for a mild to moderate form and those hospitalized for a severe form.

An information sheet was drawn up comprising several items. The determination of total 25 OHD was carried out on serum after

centrifugation by the VIDAS BioMérieux analyzer which allows the immunoenzymatic determination of 25 OHD by ELFA technique (Enzyme Linked fluorescent Assay). The vitamin D standards used for the evaluation of our results are those accepted by the majority of authors, set by the American Society of Endocrinology and the GRIPO [2] (Stand ards applied by our laboratory). SPSS 22 software was used for the statistical analysis. First, we carried out a descriptive analysis of the study population. In a second step, a univariate analysis the significance level of the statistical tests and the simple and multiple logistic regression is $p < 0.05$.

RESULTS

The analysis covers 55 children whose average age was 4.5 years old, divided into 2 groups: those hospitalized for a mild to moderate form (43 cases) and those hospitalized for a severe form (12 cases). Patients hospitalized for a mild to moderate form essentially presented digestive and respiratory symptoms. Patients hospitalized for severe forms presented: Myocarditis (2 patients), Extensive bilateral pneumonia (7 cases) and encephalitis (3 cases). The mean level of 25 OHD in the series was 13.4 ± 2.2 ng/ml.

Patients with a severe form had lower vitamin D levels than those hospitalized for a mild to moderate form (8.8 ± 0.5 ng/ml vs. 18 ± 4 ng/ml) ($p = 0.0001$) (Table 1).

Children with severe form (12/12) had vitamin D deficiency (25 OHD level below 10 ng/ml) while patients with mild to moderate form (43/43) had vitamin D deficiency. D (25 OHD level less than 20 ng/ml), no case of deficiency was noted in this group.

Table 1: Evaluation of the vitamin D status of children hospitalized for covid 19 infection.

Form COVID 19	Moderate form	Severe form
25 OHD Rate	18 ± 4 ng/ml	8.8 ± 0.5 ng/ml

DISCUSSION

In our series, patients who presented with a severe form had a lower vitamin D level than those hospitalized for a mild to moderate form (8.8 ± 0.5 ng/ml vs. 18 ± 4 ng/ml), this difference was statistically significant ($p = 0.0001$). In a systematic review of 25 randomized controlled studies, Martineau [3] described that vitamin D protected

against acute respiratory tract infections, these studies found a new echo with the COVID-19 epidemic. The pathology of COVID-19 involves a complex interaction between SARS-CoV2 and the body's immune system. Calcitriol (1,25 -dihydroxyvitamin D3) exerts pronounced impacts on the ACE2/Angiotensin axis with enhanced expression of ACE2. ACE2 is the host cell receptor responsible for mediating SARS-CoV2 infection. From this perspective, it might be obvious that the risk of infection may be higher.

Abu-Amer, et al. [4] described that vitamin D deficiency impairs the ability of macrophages to mature, produce macrophage-specific surface antigens, produce the lysosomal enzyme acid phosphatase, and secrete H₂O₂. This could explain, in part, why Martineau, et al. [3] observed that vitamin D was protective against hypovitaminosis. Receptors that recognize molecules bound to pathogens and which, when activated, release cytokines, cathelicins and defensins, are crucial in the innate immune response. The activity of several of these receptors is modulated by vitamin D induction. Several studies have notably observed a strong correlation between the levels of vitamin D and the cytokine storm observed in patients with severe forms of COVID-19. Among these publications, the one carried out in the USA (Chicago) by Lee Smith [5] who tried to identify the statistical links between vitamin D deficiency and severe forms of COVID-19 by consulting epidemiological data from different countries heavily affected by the SARS-CoV2 Coronavirus epidemic (China, France, Germany, Italy, Iran, South Korea, Spain, Switzerland, United Kingdom and the United States). It emerges from this statistical analysis that patients who were not deficient in Vitamin D presented a 14.6% risk of developing a severe form of COVID-19, while for patients deficient in Vitamin D, this risk was 29%. 6%, an increase of 15% statistically significant, these patients had twice the risk of death than people who are not deficient, which was found in our work or children with severe form (12/12) had a vitamin D deficiency (25 OHD level below 10 ng/ml) while patients with a mild to moderate form (43/43) had a vitamin D deficiency (25 OHD level below 20 ng/ml), no case of deficiency was observed in this group.

In order to assess whether there is an association between mean vitamin D levels in various countries and mortality caused by COVID-19 and to identify whether there is an association between mean vitamin D levels in various countries and the number of COVID-19 cases, A British study [6] covering 20 European countries was carried out using data from hospitals in several countries. To test this hypothesis and limit confounding bias, the study focused on European countries only. A negative correlation was between mean vitamin D levels (mean 56.79 nmol/l and number of COVID-19 cases in each country ($r = -0.4435$; p -value = 0.050), as well as mean levels. According to authors, the differences between the mortality rates linked COVID-19 from one country to another cannot be explained by the quality of the healthcare systems, by the age distribution in the population or even by the availability of tests. They noted, however, a significant correlation between mortality rates and vitamin D deficiency, in addition, levels correct of vitamin D would not prevent COVID-19 infection. They may, however, protect against the serious complications associated with it. Another study [7] suggested the

possible role of vitamin D deficiency via unregulated inflammation in COVID-19 complications by analyzing the links between high C-Reactive Protein (CRP) concentration and COVID-19 severe with adjustment for age. Since CRP is a surrogate marker for cytokine storm, the correlation between vitamin D and CRP was calculated based on 9,212 data from NHANES, this study concluded the possible role of vitamin D in reduction of complications attributable to inflammation and cytokine storm. The National Academy of Medicine [8] has issued its opinion on the subject. By concluding that this vitamin modulates the functioning of the immune system by stimulating macrophages and dendritic cells and plays a role in the regulation and suppression of the cytokine inflammatory response at the origin of the acute respiratory distress syndrome which characterizes the severe forms and often lethal from COVID-19. Therefore, she recommends "promptly measuring serum vitamin D levels (i.e. 25 OHD) in people over the age of 60 with COVID-19, and to administer, in the event of a deficiency, a loading dose of 50,000 to 100,000 IU which could contribute to limiting respiratory complications and to provide vitamin D supplementation of 800 to 1000 IU/day in people aged under 60 years from the confirmation of the diagnosis of COVID-19 [8].

CONCLUSION

Vitamin D deficiencies are clearly detrimental to the immune system. The severity of COVID-19 infection is caused, besides viral virulence, by the release of pro-inflammatory cytokines. An optimal level of vitamin D in the body could protect patients against serious complications of COVID-19 infection. If these observational data were to be confirmed by randomized trials, vitamin D could constitute an additional therapeutic weapon.

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