e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2024; 16(1); 221-225

Original Research Article

A Case Control Assessment of the Association of Serum Vitamin D (25(OH) D) Level and Recurrent Wheeze in Children Less Than Five Years of Age

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Received: 15-11-2023 Revised: 19-12-2023 Accepted: 14-01-2024
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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to assess the association of serum vitamin D (25(OH) D) level and recurrent wheeze in children less than five years of age.

Methods: This was a hospital-based analytical case-control study performed in the Pediatrics department of Darbhanga Medical College and Hospital. Children less than five years of age, diagnosed with recurrent wheeze, presenting to emergency/outpatient department were enrolled after getting written informed consent. A total of 50 cases with recurrent wheeze along with 50 healthy controls were enrolled.

Results: The basic demographic characteristics i.e., age, sex, weight, and height was comparable in both the groups. Moreover, both the groups had very less but comparable sunlight exposure. The feeding pattern was significantly different between two groups. Most of the cases (64%) were exclusively and prolonged breastfed in contrast to controls in which most (72%) of the babies were started on complementary feeds at six months. There were no seasonal variations in the frequency of wheezing. The mean serum levels of 25-hydroxyvitamin D, calcium, and inorganic phosphate were significantly higher in controls compared to cases. Conversely, median serum ALP was significantly more in cases than the controls. Among them too, serum vitamin D and ALP levels were significantly different in cases and control. Most of the babies were exclusively breastfed until six months, however complementary feeding was not initiated at six months of age in most.

Conclusion: Low serum 25(OH)D levels are strongly associated with recurrent wheezing in preschool children. In absence of vitamin D levels, high serum alkaline phosphatase levels (>350 IU/L) can be used as a predictor of recurrent wheeze. However, breastfeeding doesn't seem to protect against recurrent wheezing.

Keywords: Alkaline phosphatase, Asthma, Calcium, Phosphate

Introduction

Studies in animal models and humans have demonstrated an association of low vitamin D concentrations with atopy and respiratory tract conditions. The mechanism that explains this association is still unclear. It has been suggested that this mechanism is due to the effects of vitamin D status on the regulation of the immune system. [1] The vitamin D receptor is expressed in various cells of the immune system, such as macrophages, monocytes, dendritic cells, and natural killer cells, as well as in B and T lymphocytes. Binding of the active form of vitamin D to its receptor leads to an increase in immunomodulatory activity that maintains the balance between the cellular immune response (Th1) and the humoral response (Th2), in addition to stimulating regulatory T cells. [2]

The prevalence of atopic diseases, especially chronic respiratory diseases, such as asthma and recurrent wheezing in childhood, is increasing both in Brazil and worldwide. These diseases represent an important cause of morbidity and mortality in the pediatric age group. They are considered a public health problem because they affect the quality of life of these patients, given frequent use of the health care system, causing great economic impact. [3,4] Various risk factors are associated with recurrent wheezing and asthma: small airway caliber; decreased lung function at birth; viral respiratory

infections; environmental pollution; pets; early daycare attendance; passive smoking; parental history of asthma or atopy; obesity; and socioeconomic factors. In this context, vitamin D plays a prominent role as a risk factor for increased prevalence of allergic diseases. [5]

Serum 25OHD is the best indicator of vitamin D status in body. Vitamin D deficiency has a high incidence worldwide. It is estimated that almost half of the healthy people are 25 OHD deficient. [6] Insufficient sun exposure or pigmented skin and inadequate dietary intake are the main causes of these low levels of vitamin D. There has been growing recognition of the extra skeletal role of vitamin D in recent years. Vitamin D plays a significant role in inborn and adaptive immunity. [7,8] It was documented that the global rise of asthma and allergic diseases may be linked to lower vitamin D. [9,10] The greatest burden of allergic diseases is during childhood at which time the rapidly rising rates of diseases are most evident in population. Recurrent wheezing in young children either transient or that will continue as asthma, can be severe and cause significant impairment in quality of life with frequent visits to health professionals. [11,12] It is estimated that about one third of school age children manifest the wheezing during the first 5 years of life. [11]

The aim of the present study was to assess the association of serum vitamin D (25(OH) D) level and recurrent wheeze in children less than five years of age.

Materials and Methods

This was a hospital-based analytical case-control study performed in the Department of Pediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India for one year. Children less than five years of age, diagnosed with recurrent wheeze, presenting to emergency/outpatient department were enrolled after getting written informed consent. A total of 50 cases with recurrent wheeze along with 50 healthy controls were enrolled. Those with underlying chronic/ prolonged medical or surgical illness, clinical rickets received vitamin D supplementation in last six months or congenital malformations were excluded. Healthy age and weight matched children visiting outdoors for immunization or routine check-up were taken as controls.

Detailed history of wheezing episodes along with therapy, dietary history, sunlight exposure, respiratory system examination and anthropometry using WHO growth charts were recorded. [13] The study was approved by the Institute ethics committee. Blood samples (2 mL) were taken in two plain vials. Subsequently, serum was separated by in-house centrifuge machine and was stored at -4°C. Serum analysis for 25(OH)D, calcium, inorganic phosphate, and alkaline phosphatase was done on the same day. Serum 25 (OH) D was measured by an ELISA kit from DLD Diagnostika GMBH (Alder host, Hamburg, Germany). Serum 25(OH) D level of >20 ng/mL was considered sufficient, level between 12-20 ng/mL as insufficient, and <12 ng/mL was considered as deficient. [14,15] Recurrent early wheeze was defined as >2 reports of wheezing in the first 3 years of life. [16]

Statistical Analysis

Data were collected on structured proforma and managed using Microsoft Excel spreadsheets. Subsequently, SPSS software version 20.0 was used for statistical analysis. Descriptive statistic was used for the characteristics of the study subjects. Comparison of continuous variables across two groups was done using Student's t-test or Mann-Whitney U test. Statistical significance of categorical variables was determined by Chi-square test or Fischer-Exact test. Spearman rank correlation was calculated to find the strength of the relationship between various quantitative variables (vitamin D and ALP). A p-value of less than 0.05 was considered statistically significant.

Results

Table 1: Baseline characteristics

Parameter	Cases (n-50)	Controls (n-50)	p-value
Age (months) Mean (SD)	17 (8.2)	21.9 (8.5)	0.2
Male n (%)	25 (50)	24 (48)	0.5
Weight (kg) Mean (SD)	11.48 (1.8)	12.78 (3.4)	0.07
Length (cms) Mean (SD)	80.50 (8.4)	81.12 (8.8)	0.5
Exclusively breastfed until 6 month of age n (%)	32 (64)	20 (40)	0.007
Complementary feeding: Started at 6 months n (%)	17 (34)	36 (72)	<0.001
Sunlight Exposure <30 min/ week n (%)	36 (72)	34 (68)	0.2

The basic demographic characteristics i.e., age, sex, weight, and height was comparable in both the groups. Moreover, both the groups had very less but comparable sunlight exposure. The feeding pattern was significantly different between two groups. Most of the cases (64%) were exclusively and prolonged breastfed in contrast to controls in which most (72%) of the babies were started on complementary feeds at six months. There were no seasonal variations in the frequency of wheezing.

Table 2: Comparison of biochemical parameters among cases and controls

Parameter	Cases (n-50)	Controls (n-50)	p-value
Vitamin D level (ng/mL) Mean (SD)	18.84 (4.8)	26.24 (3.2)	<0.001
Calcium (mg/dL) Mean (SD)	8.62 (1.74)	9.45 (1.42)	0.007
Inorganic phosphate (mg/dL) Mean(SD)	4.86 (1.34)	5.65 (1.42)	<0.001
Alkaline phosphatase (IU/L) Median(1^{st}, 3^{rd} quartile)	678 (478-819)	316 (165-581)	<0.001
Vitamin D insufficiency (<20 ng/mL)n (%)	37 (74)	20 (40)	<0.001
Vitamin D deficiency (<12 ng/mL)n (%)	11 (22)	3 (1.5)	<0.001

The mean serum levels of 25-hydroxyvitamin D, calcium, and inorganic phosphate were significantly higher in controls compared to cases. Conversely, median serum ALP was significantly more in cases than the controls.

Table 3: Analysis of subjects with vitamin D insufficiency

Parameter	Cases (n-37)	Control (n-20)	p-value
Sunlight exposure of <30 min/weekn (%)	30	16	0.7
Exclusively breast fed until sixmonths n (%)	29	14	0.5
Complementary feeding initiated atsix months of age n (%)	8	8	0.1
Serum Vitamin D level (ng/mL)Mean (SD)	11.5 (4.7)	14.6 (2.4)	<0.001
Serum Alkaline phosphatase level(IU/L) Mean (SD)	840.18 (342.2)	618.42 (282.2)	0.005
Serum Alkaline phosphatase>350IU/L n (%)	32	15	0.07

Among them too, serum vitamin D and ALP levels were significantly different in cases and control. Most of the babies were exclusively breastfed until six months, however complementary feeding was not initiated at six months of age in most.

Discussion

About one in every three children have at least one episode of wheezing prior to their third birthday and cumulative prevalence of wheeze is around 50% at six years of age. [16-18] Recurrent wheeze is defined as three or more episodes of parentally reported wheeze in the past 12 months of life.[18] Its occurrence is quite common and is reported in 6.2% of the Indian children. [19] Although there are many risk factors responsible for the development of recurrent wheezing, recently, vitamin D has gained significant interest. Studies reported that low vitamin D levels even in cord blood may be responsible for many childhood diseases. [20,21]

Vitamin D deficiency is a global health problem. It has been reported that the prevalence of vitamin D deficiency ranges from 69% - 82% in Indian population. [22] The high frequency of vitamin D deficiency in our country may be related to inadequate vitamin D supplementation during infancy, low levels of vitamin D during pregnancy and scarcity of vitamin D fortified food products. [23] Studies conducted in Finland and Japan on more than 750 mother child pair have found that dietary vitamin D intake is inversely related to the incidence of wheezing in children. [24] Sunlight exposure is an important factor in vitamin D synthesis. The limited exposure seems to be due to change in life style. Studies have shown that a minimum 30 minute weekly sunlight exposure in bright sunlight over 40 % body area for at least four months is required to achieve sufficient vitamin D by 6 months of age in breast fed infants. [25,26] The basic demographic characteristics i.e., age, sex, weight, and height was comparable in both the groups. Moreover, both the groups had very less but comparable sunlight exposure. The feeding pattern was significantly different between two groups. Most of the cases (64%) were exclusively and prolonged breastfed in contrast to controls in which most (72%) of the babies were started on complementary feeds at six months. There were no seasonal variations in the frequency of wheezing. Vitamin D has an important role in the lung development and regulation of innate and adaptive immunity. [27,28] A significant association exists between the number of vitamin D receptors genes and the respiratory syncytial virus bronchiolitis. [29] Conversely, serum 25(OH)D levels are inversely related to respiratory viral infections in children. [30] So, there is enough evidence to conclude that vitamin D plays an important role in respiratory diseases like asthma and wheeze in children.

The mean serum levels of 25-hydroxyvitamin D, calcium, and inorganic phosphate were significantly higher in controls compared to cases. Conversely, median serum ALP was significantly more in cases than the controls. Among them too, serum vitamin

D and ALP levels were significantly different in cases and control. Most of the babies were exclusively breastfed until six months, however complementary feeding was not initiated at six months of age in most. Studies have shown that a minimum 30- minute weekly sunlight exposure in bright sunlight, over 40% body area for at least four months is required to achieve sufficient vitamin D levels by six months of age. [25] Kumar et al reported that serum vitamin D level below 17.5 ng/ml predisposes for recurrent wheezing episodes and decrease in its level by 1ng/ml in serum increases the chances of wheezing by 7.3%. [31] In 2014 Stenberg Hammer et al demonstrated that subnormal levels of vitamin D are associated with acute wheeze in preschool children. [32]

Conclusion

Low serum 25(OH)D levels are strongly associated with recurrent wheezing in preschool children. In absence of vitamin D levels, high serum alkaline phosphatase levels (>350 IU/L) can be used as a predictor of recurrent wheeze. However, breastfeeding doesn't seem to protect against recurrent wheezing.

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