Original Article

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Paediatrics Section

A Hospital Based Study to Establish the Correlation between Recurrent Wheeze and Vitamin D Deficiency Among Children of Age Group Less than 3 Years in Indian Scenario

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ABSTRACT

Introduction: Early childhood wheezing is a heterogeneous condition, which has several phenotypic expressions and a complex relationship with the development of asthma later in life. New studies indicate the prevalence of recurrent wheeze to be associated with Vitamin D deficiency. This has not been explored in Indian settings widely, mandating this exploration.

Aim: To determine the severity of Vitamin D deficiency and its association with recurrent wheeze in children less than 3 years of age.

Materials and Methods: Consecutive type of non-probability sampling was followed for selection of study subjects with a total sample size to be 122 children in the Hospital setting. A pre- formed, pre- tested, structured interview schedule was used to obtain information. Estimation of 25 (OH) Vitamin D was done using ELISA method. Kit used for estimation was DLD Diagnostika GMBH 25(OH) Vitamin D ELISA from Germany. Standard statistical tools were used including Logistic regression analysis, and ROC curve, p value <0.05 was considered to be statistically significant. SPSS software version 17.0 was used.

Results: Each 10ng/ml decrease in Vitamin D level is associated with 7.25% greater odds of wheezing. Our study also suggests, exclusive breast feeding and delaying of complementary feeding beyond 6 months of age are significant predictors of Vitamin D deficiency and have indirect association with increased incidence of wheezing in children.

Conclusion: The study concluded that Vitamin D deficiency is associated with increased risk of recurrent wheezing.

Keywords: Delayed complementary feed, Early childhood, Exclusive breast feeding, Logistic regression analysis, Predictors

INTRODUCTION

Wheezing is a very common respiratory symptom during childhood. Epidemiological studies have reported that almost one-third of all children wheeze at least once in the first three years of life, with nearly 50% of all children having at least one wheezing episode by the age of 6 years [1-3]. However, early childhood wheezing is a heterogeneous condition, which has several phenotypic expressions and a complex relationship with the development of asthma later in life [4]. Wheeze is defined as continuous high pitched sound with musical quality emitting from the chest during expiration which lasts for more than 250 msec [5].

Low serum 25-hydroxy vitamin D levels have been associated with increased risk of lower respiratory tract infections in young children as has been shown by various epidemiologic studies [6,7]. Adding on, evidence is there suggesting enhanced risk of childhood wheezing associated with low levels of maternal intake of vitamin D during pregnancy and umbilical cord blood 25(OH)D [6,8]. Various interventional trials support these associations by establishing lowered respiratory tract infections in children having vitamin D supplementation [9,10].

Recurrent wheeze is defined as three or more episodes of parentally reported wheeze in the past 12 months of life [1]. The prevalence of wheeze is 6.2% in India [11]. Studies suggest reasons for newborns with low serum vitamin D including low sun exposure, no food fortification of Vitamin D, month of being born, history of asthma and young maternal age [12]. Evidence suggest lower the amount of Vitamin D, the higher the risk for wheezing [13].

Differential Diagnosis of Wheezing includes long list including infections, asthma, anatomic abnormalities like TEF, vascular ring, Broncho-pulmonary dysplasia, Aspiration syndromes, Interstitial lung disease, often making it hard to pin point the reason [14]. Although there are many risk factors for development of recurrent wheezing [15,16] an emerging risk factor of particular interests is Vitamin D status [17]. The evidence for the possible link between vitamin D and respiratory disease comes from multiple studies [18-21]. Role of maternal vitamin D uptake and its relation to wheezing in early childhood also has been probed [22]. In the Childhood Asthma Management Program (CAMP) [23] those with low baseline 25(OH) Vitamin D levels (< 75nmol/L) were more likely to have a severe asthma exacerbation over a 4 months period [24].

Vitamin D present in various forms including 1α, 25(OH_2) D_3 and its role in humans has been studied in detail, its role has been well established in the demineralization process of bone, mediated by intricate balance of serum calcium, phosphorus and Vitamin D as a hormone and its defeciency leading to rickets among children and osteomalacia in Adults [25]. Its role in gene mediated expression of Bronchial smooth muscle cell following 1α, 25(OH_2) D stimulation also has been probed [26]. Studies have shown the role of Vitamin D in genetic related cell movement important for airway remodeling. Its other form 1α, 25(OH_2) D_3 induces genes in Ca related pathways leading to bronchial smooth muscle contraction [27-31].

Contrary to the belief, the data available in published literature suggests Vitamin D deficiency is very common in India in all the age groups and both the sexes across the country [32-35].

In our hospital setup, we have found that large number of wheezy children was presenting with florid rickets and signs of Vitamin D deficiency but no other causes of wheeze were found on investigation. Our study has been proposed to find out the association between

Vitamin D deficiency and recurrent wheeze in children less than 3 years of age.

AIM

To determine the severity of Vitamin D deficiency and its association with recurrent wheeze in children less than 3 years of age.

MATERIALS AND METHODS

To study the serum levels of Vitamin D in recurrent wheezy children less than 3 years of age and their age matched controls.

Study Hypothesis: "Vitamin D deficiency is associated with recurrent wheezing in children below 3 years of age and its levels are significantly lower in these children."

Setting: This study was a Hospital based case control study conducted in the Department of Paediatrics, Lokmanya Tilak Municipal Medical College & General hospital, a tertiary care hospital in Mumbai. From June 2013 to May 2014. Consecutive type of non-probability sampling was followed for selection of study subjects, with a case sample size of 61 and similar number of controls fulfilling inclusion and exclusion criteria who gave informed consent to participate in study were enrolled with a total sample size of 122 (61 cases and 61 controls). Exclusive Breast Feeding remains the mainstay of infant feed, and we in our study also took history of breast feeding and tried to explore its impact on Vitamin D levels. Breastfeeding was categorized as exclusive breastfeeding for 1st 6 months of life and after six month on complementary feed i.e. on breast milk and other feed. Clearance from Ethical committee in College was taken.

Inclusion criterion: Children <3 years of age, who had 3 or more episodes of wheeze (recurrent wheezers) in the past 12 months without any obvious cause were included in study. For control group, same number of less than 3 years of age children who came to OPD/paediatric emergency for minor and nonspecific complain were included. Children whose parents were willing to participate in the study. A written informed consent was obtained from the parents for enrolling their child for the study.

Exclusion Criteria: Children with history of intake of vitamin D supplementation and children with known causes of wheezing were excluded.

A pre-formed, pre-tested, structured interview schedule was used to obtain information from all study subjects. A detailed history and clinical examination was done for each child.

Breastfeeding history was recorded. Breastfeeding was categorized as exclusive breastfeeding for 1st 6 months of life and after six month on complementary feed i.e. on breast milk and other feed.

Vitamin D Estimation: Kit used for estimation is DLD Diagnostika GMBH 25(OH) Vitamin D ELISA from Germany. Standard Definition of Vitamin D and its deficiency were used [36].

STATISTICAL ANALYSIS

All the collected data was entered in Microsoft Excel sheet after generation of proper template. It was then transferred to SPSS version 17 software for statistical analysis.

RESULTS

Very severe Vitamin D deficiency (< 5ng/ml) was observed in 23% of cases while none had vitamin D levels above 30 ng/ml. Optimum levels were observed in 44.3% of controls while none had levels below 10 ng/ml. Significantly lower levels of Vitamin D were observed in cases compared to controls (p< 0.05) [Table-Fig-1].

On observing the distribution of various laboratory parameters, we found that controls had significantly greater mean Vitamin D (31 vs. 11.6 ng/ml) and S. calcium (9.2 vs. 8.9 mg/dl) values. The difference was statistically significant (p<0.05) Alkaline Phosphatase levels were significantly higher in cases than controls (585.4 vs. 302.1 IU/L). The difference was statistically significant (p<0.01) [Table-Fig-2].

On analysing data with binary logistic regression we found that Vitamin D levels significantly predicts the occurrence of Wheezing (p < 0.05; Odds Ratio - 0.7). Each 10 ng/ml decrease in vitamin D was associated with 7.25% greater odds of current wheeze. Area under ROC curve for vitamin D levels as a test for diagnosing wheezing is 0.965.(p<0.05) Area under ROC curve for vitamin D levels as a test for diagnosing wheezing is 0.965 (p<0.05) [Table-Fig-3]. Area under

Vitamin D Levels (ng/ml)		Group		Total
		Cases	Controls	
Very Severe deficiency (< 5)	N	14	0	14
	%	23.00%	0.00%	11.50%
Moderate deficiency (5-9.9)	N	23	0	23
	%	37.70%	0.00%	18.90%
Deficiency (10-19.9)	N	8	7	15
	%	13.10%	11.50%	12.30%
Insufficiency (20-29.9)	N	16	27	43
	%	26.20%	44.30%	35.20%
Optimal Level (≥ 30)	N	0	27	27
	%	0.00%	44.30%	22.10%
Total	N	61	61	122
	%	100.00%	100.00%	100.00%

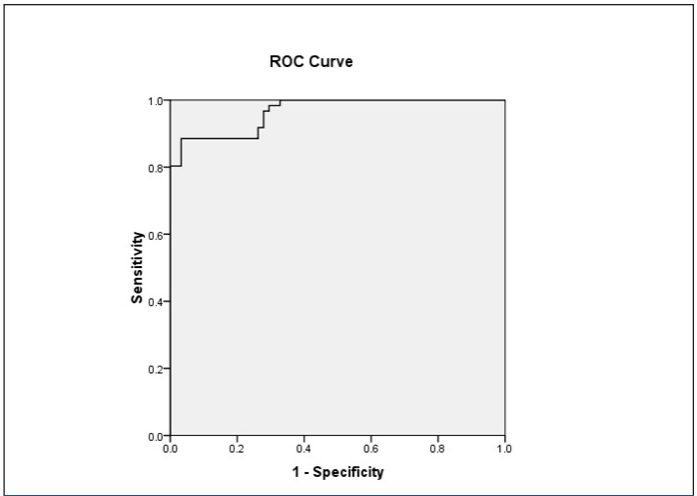
[Table/Fig-1]: Distribution of Subjects based on Vitamin D levels.
p- value < 0.05*, *Chi-Square test

Variables (n-122)	Group	N	Mean	Std. Deviation	p-value
Vitamin D (ng/ml)	Cases	61	11.6	7.4	< 0.05
	Controls	61	31.0	8.7	
Calcium (mg/dl)	Cases	61	8.9	0.7	< 0.05
	Controls	61	9.2	0.7	
Inorganic Phosphorus (mg/dl)	Cases	61	4.2	1.3	0.34
	Controls	61	4.5	1.3	
Alkaline Phosphatase (IU/L)	Cases	61	585.4	447.1	< 0.01
	Controls	61	302.1	138.4	

[Table/Fig-2]: Distribution of Subjects based on Mean Laboratory Parameters.
p- value < 0.05*, *Chi-Square test

Binary Logistic Regression	B	S.E.	Wald	Df	p-value	Odds Ratio
Vitamin D Levels	-0.322	0.064	25.613	1	< 0.05	0.725
Constant	6.955	1.481	22.048	1	< 0.05	1048.504

[Table/Fig-3]: Binary Logistic regression matrix to predict Wheezing with Vitamin D as Dependent variable.



[Table/Fig-4]: Receiver Operating Characteristic (ROC) Curve for Vitamin D.

No. of wheezing attacks/ year		Vitamin D levels				Total
		< 5	5-9.9	10-19.9	20-29.9	
Three	N	7	12	3	9	31
	%	50.00%	52.20%	37.50%	56.20%	50.80%
Four	N	4	8	5	7	24
	%	28.60%	34.80%	62.50%	43.80%	39.30%
Five	N	3	3	0	0	6
	%	21.40%	13.00%	0.00%	0.00%	9.80%
Total	N	14	23	8	16	61
	%	100.00%	100.00%	100.00%	100.00%	100.00%

[Table/Fig-5]: Association of Vitamin D levels and wheezing.
p- value -0.35*, *Chi-Square test

Variable	Code	
Sun Exposure (> 30 minutes/ week)	Yes	1
	No	0
Exclusive Breast Feeding till 6 months	Yes	1
	No	0
Complementary Feeding started at 6 months	Yes	1
	No	0

[Table/Fig-6]: Linear regression matrix to find predictors of Vitamin D deficiency.

Variables	Unstandardized Coefficients		Standardized Coefficients	t	p-value
	B	Std. Error	Beta		
Sun Exposure (> 30 minutes)	11.791	3.125	0.468	3.773	< 0.001
Exclusive Breast Feeding till 6 months	0.601	2.84	0.024	0.212	0.833
Complementary Feeding started at 6 months	9.221	3.046	0.366	3.028	0.003

[Table/Fig-7]: Linear Regression Model
a. Dependent Variable: Vitamin D

ROC curve for vitamin D levels as a test for diagnosing wheezing is 0.965. (p<0.05) [Table-Fig-4].

[Table-Fig-5] Shows that there was no significant association between severity of vitamin D deficiency levels and frequency of wheezing attacks [Table-Fig-4]. On analysing data with linear regression model, we observed that sun exposure for less than 30 minutes/ week, and delaying of complementary feeding beyond 6 months were significant [Table-Fig-6,7].

DISCUSSION

In recent years, vitamin D has been a focus of growing interest in public health nutrition. Studies suggesting prevalence of Vitamin D deficiency in India in Epidemic proportions [35]. The most possible solution seems to be food fortification in Wheat, Curd, Flour ghee etc. Vitamin D deficiency is associated with increased risk of recurrent Wheezing, Vitamin D can significantly predict the occurrence of recurrent wheezing. Each 10ng/ml decrease in Vitamin D level is associated with 7.25% greater odds of wheezing. Considering the deficiency of vitamin D, among cases and controls as per our study, vitamin D supplementation may be considered even in healthy children because children may not have any classical clinical feature of rickets. Sun exposure less than 30 minutes/week is significant predictor of Vitamin D deficiency and is indirectly associated with increased risk of recurrent wheezing.

Laboratory research suggests several potential mechanisms for how vitamin D can affect risk of asthma. Many recent studies of genetic association [18,19,37-39] suggest about relation of polymorphisms of VDR gene to obstructive pulmonary disease.

Very severe Vitamin D deficiency (< 5ng/ml) was observed in 23% of cases while none had vitamin D levels above 30 ng/ml [Table/Fig-1]. Data was statistically significant (p<0.05). Optimum levels were observed in 44.3% of controls while none had levels below 10 ng/ml. [Table/Fig-1]. Mean Vitamin D level was significantly lower in cases compared to controls (11.6 vs. 31 ng/ml). On analysing data with binary logistic regression we also found that Vitamin D levels can significantly predicts the occurrence of Wheezing in children (Odds Ratio - 0.7, AROC – 0.96) [Table/Fig-3&5] & [Table/Fig-4] ROC. Each 10 ng/ml decrease in vitamin D was associated with 7.25% greater odds of current wheeze.

In studies [9,23] higher maternal intake of Vitamin D was linked to a reduced frequency of wheezing in early childhood. Elsewhere it was concluded that cord-blood levels of 25 (OH) vitamin D had inverse associations with risk of respiratory infection and childhood wheezing [6]

Similarly Keet et al., concluded, each 10 ng/mL decrease in vitamin D was associated with a 26% greater odds (OR: 1.26 {95% CI: 1.09–1.46}) of current wheeze [40].

In a study Graham D et al., selected subjects from a birth cohort recruited in utero with the primary objective of identifying associations between maternal diet during pregnancy and asthma and allergies in children. They concluded that increasing maternal vitamin D intakes during pregnancy may decrease the risk of wheeze symptoms in early childhood [22].

S. Calcium levels in cases and controls were 8.9 and 9.2 mg/dl (p< 0.05) [Table/Fig-2]. Alkaline Phosphate levels were significantly higher in cases than controls (585.4 vs. 302.1 IU/L) (p<0.01). [Table/Fig-2]. The results can be explained on the basis of various studies showing direct positive co-relation of vitamin D levels with Calcium [41-43] and its negative co-relation with alkaline phosphatase levels [44-46].

In [Table/Fig-6,7], we also observed that sun exposure for less than 30 minutes/week, and delaying of complementary feeding beyond 6 months were significant predictors of vitamin D deficiency (p< 0.01).

LIMITATIONS

Small sample size and no IgE level estimation.

RECOMMENDATIONS

Massive health education campaigns are needed to guide women about importance of proper nutrition during pregnancy and adequate sunlight exposure. Measurement of Vitamin D level should be included in the workup of recurrent wheezing children. But a larger study is needed for more confirmation as the test is very costly. There is also need to develop recommendations for vitamin D supplementation for pregnant and lactating women also; this is another possible strategy for improving vitamin D status.

CONCLUSION

We conclude that exclusive breast feeding and delaying of complementary feeding beyond 6 months of age are significant predictors of Vitamin D deficiency and have indirect association with increased incidence of wheezing in children.

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