European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 9, Issue 3, Winter 2022

ORIGINAL RESEARCH

A Hospital Based Comparative Study to Evaluate the Association of Acute Respiratory Tract Infections with Serum Vitamin-D Levels in Children Between 2 Months to 5 Years of Age

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ABSTRACT

Background: Vitamin D has long been known to play a role in the skeletal system and calcium homeostasis; the deficiency of which causes rickets and osteoporosis. There is growing evidence that vitamin D also contributes positively to pulmonary health. Vitamin D deficiency is a common and important nutritional deficiency in children in India. Clinical and subclinical vitamin D deficiency in children has been reported to be a significant risk factor for severe acute respiratory tract infection. The aim of this study to compare the evaluation of the association of acute respiratory tract infections with serum vitamin-D levels in children between 2 months to 5 years of age.

Materials& Methods: A hospital based prospective study done on 50 children with ARTI aged between two months and five years fulfilling the inclusion criteria attending the Department of Paediatrics at JNUIMSRC, Jaipur, Rajasthan, India during one year study period. ARTI as defined by revised classification and treatment of childhood pneumonia under Integrated management of neonatal and childhood illnesses (IMNCI). Vitamin D levels were classified as per the Endocrine Society recommendations in which vitamin D deficiency was defined as a 25(OH) D3 level of 20 ng/mL or less, 21 to 29 ng/mL as insufficient and 30 ng/mL or greater as sufficient. Chi-square test was used as test of significance for qualitative data. P-value of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Results: Among the group with insufficient serum vitamin D levels, majority (55.17%) were in the age group of 2-12 months. Association of ARTI cases according to socio economic status and serum vitamin D levels was found to be statistically significant (p<0.05*).It was observed that in the group with sufficient serum vitamin D levels, majority (75%) were exclusively breast fed while 25% received combined feeding. We showed that in those subjects with sufficient serumVitamin D levels, 50% had no pneumonia while pneumonia and severe pneumoniawas present in only 25% each. In the group with insufficient serum Vitamin Dlevels, 62.06% had pneumonia while 17.24% had severe pneumonia. In the group withdeficientserumVitaminDlevels,64.70%hadseverepneumoniawhile23.52%hadpneumonia.Thus,pneumoniaandseverepneumoniawasfoundinincreasingfrequency in children

with insufficient and deficient serum Vitamin D levels whichwasstatisticallysignificant (P<0.05*)

Conclusion: We conclude that deficiency of vitamin D is a modifiable risk factor in prevention of ARTI. Vitamin D supplementation should be advocated in order to prevent the morbidity and mortality secondary to ARTI, which globally contribute to morbidity worldwide.

Keywords: ARTI, Vitamin D, Sun exposure, Children.

INTRODUCTION

Acute respiratory tract infection (ARTI) is a major public health problem worldwide. ARTI is a substantial cause of morbidity and mortality in young children, in both developed and developing countries. ARTI is an acute infection of any part of respiratory tract and related structures including paranasal sinuses, middle ear and pleural cavity.[1] In young children, ARTI is responsible for an estimated 3.9 million deaths worldwide, with 90% deaths due to bacterial pneumonia. In the developing countries, seven out of 10 deaths happen due to ARTI in under 5-year age group.[1]

In India, about 26.3 million cases of ARTI were reported in 2011, with an incidence rate of about 2,173 cases per lakh population.[2] ARTI contributes to 15-30% of all under five deaths in India and most of these deaths are preventable.[2]A number of social and environmental factors are associated with ARTI morbidity and mortality in childhood. Various risk factors associated with ARTI are poverty, malnutrition, low birth weight, inadequate breast feeding, overcrowding, poor housing conditions, micronutrient deficiency, indoor and outdoor air pollution.[3] Various steps have been taken for the prevention and control of ARTI all over the world which include exclusive breast feeding up to six months of age, vaccinations, providing adequate nutrition, encouraging hand washing and intake of micronutrients like zinc.[4,5] Vitamin D deficiency is a common and important nutritional deficiency of children in India. Clinical and subclinical vitamin D deficiency in children has been reported to be a significant risk factor for severe ARTI. Studies have shown that incidence of ARTI are more in individuals who have lower levels of vitamin D.[6] Respiratory illnesses, like asthma, have a greater risk of developing with low levels of vitamin D.[7] There have been many studies to suggest that subclinical Vitamin D deficient levels predisposes to ARTI[8-10] but seldom studies have been done to associate the serum levels of Vitamin D and severity of ARTI.

The major role of vitamin D is bone mineralization and calcium metabolism, by way of its endocrine like actions. But recently Vitamin D is found to have many other roles in the body, including modulation of cell growth & immune function and reduction of inflammation.[11] With the recent links between vitamin D and immune function, there has been increasing interest in the role of vitamin D in respiratory infections. In some observational studies, it was observed that low vitamin D level in blood is associated with the increased incidence of respiratory tract infections.[8]The aim of this study to compare the evaluation of the association of acute respiratory tract infections with serum vitamin-D levels in children between 2 months to 5 years of age.

MATERIALS& METHODS

A hospital based prospective study done on 50 children with ARTI aged between two months and five years fulfilling the inclusion criteria attending the Department of Paediatrics at Jaipur National University Institute for Medical Sciences & Research Centre (JNUIMSRC), Jaipur, Rajasthan, India during one year study period.

INCLUSION CRITERIA

ARTI as defined by revised classification and treatment of childhood pneumonia under Integrated management of neonatal and childhood illnesses (IMNCI)[12] as described below were included in the study.

- No Pneumonia: Cough or cold (by history) and no fast breathing.
- Pneumonia:Cough or difficulty breathing (by history) and chest in-drawing (fast breathing: number of breaths in one minute for 2-12 months as > 50 breaths per minute; 12 months -5 years fast breathing >40 breaths per minute)
- Severe Pneumonia / Very Severe Disease: Cough or chest in drawing or stridor in a calm childor difficulty breathing and any general danger signs like inability to feed, lethargy, cyanosis).

EXCLUSION CRITERIA

1. Children already on vitamin D supplementation.
2. Children with clinical rickets.
3. Protein energy malnutrition.
4. Congenital heart diseases.

METHODS

Children were evaluated with a detailed clinical history (nature and duration of symptoms) and background characteristics including feeding practices (breastfeeding history and age of introduction of complementary foods), immunization status, and socio-demographic variables such as the parental education, occupation, family income, details of cooking fuel used in the household, family history of smoking, and history of lower RTI in the past. Information was collected regarding the practice of exposure of the child to sunlight. A semi-structured proforma was prepared. Based on severity of ARTI, patients were classified according to the IMCI criteria.[12]

Information regarding the practice of exposure of the child to sunlight was collected including the frequency and approximate duration of sun exposure. History of smoking by various members in the family and details of cooking fuel used were recorded. A detailed clinical examination was performed. Length of the child was measured on an infantometer to the nearest centimeter till the age of two years and thereafter height on a stadiometer. Weight of the child was recorded on beam type of weighing scale to the nearest 100 g. Children were examined for pallor and was labelled as anaemia if pallor was present in the conjunctiva and/or mucous membrane and/or colour of palmar creases was similar to the rest of the palm and are counted as exclusion criteria.[13]

Two ml of venous blood sample was drawn for estimation of Vitamin D (25[OH] D3) levels. ELISA kit method was used for assessing vitamin D status. Vitamin D levels were classified as per the Endocrine Society recommendations in which vitamin D deficiency was defined as a 25(OH)D3 level of 20 ng/mL or less, 21 to 29 ng/mL as insufficient and 30 ng/mL or greater as sufficient.[14]

All children with deficient Vitamin D levels (≤ 20ng/ml) received Vitamin D supplementation as per Stoss regimen.[15] All other children received the recommended Vitamin D supplements of 400 IU/day.

STATISTICAL ANALYSIS

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Chi-square test was used as test of significance for qualitative data. P-value of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

RESULTS

Among the group with insufficient serum vitamin D levels, majority (55.17%) were in the age group of 2-12months while 5 (17.24%) and 4 (13.80%) subjects were in the age groups of 13-24 months and 25-36 months respectively. Among the group with deficient serum vitamin D levels, approx half (47.05%) of them were in the age group of 2- 12 months. The other 50% were distributed among the other age groups. None of the children above 25 months had sufficient serum vitamin D levels. However, it was not significant statistically.

In the group with insufficient vitamin D levels, 62.06% of subjects were males while 37.93% were females. While in the group with deficient serum vitamin D levels, majority (71.42%) were males. However, there was no significant association between Vitamin D status and gender distribution. Association of ARTI cases according to socio economic status and serum vitamin D levels was found to be statistically significant ($p<0.05^*$).It was observed that in the group with sufficient serum vitamin D levels, majority (75%) were exclusively breast fed while 25% received combined feeding.

In the group with sufficient vitamin D levels, 50% of children were exposed to 1-2hours of sunlight per day. The deficient serum vitamin D levels,71.42% received 3-4 hrs exposure to sunlight per day while 17.64% and 11.76% received 5-6 hours and >6 hours of sunlight exposure per day. The association was found to be statistically significant ($P<0.05^*$) (table 1).

Table 1: The correlation of demographic profile of patients with serum vitamin D levels

Demographic profile	Vitamin D Levels			$\chi 2$ VALUE	P-value
	Sufficient ≥30ng/ml (N=4)	In sufficient 21-29ng/ml (N=29)	Deficient ≤20ng/ml (N=17)		
Age (month)					
2-12 months	3 (75%)	16 (55.17%)	8 (47.05%)	2.68	>0.05
13-24 months	1 (25%)	5 (17.24%)	4 (23.52%)		
25-36 months	0 (0%)	4 (13.80%)	2 (11.76%)		
37-48 months	0 (0%)	2 (6.90%)	1 (5.88%)		
49-60 months	0 (0%)	2 (6.90%)	2 (11.76%)		
Gender					
Male	2 (50%)	18 (62.06%)	10 (71.42%)	0.645	>0.05
Female	2 (50%)	11 (37.93%)	7 (41.18%)		
Socio economic status					
Upper class	1 (25%)	1 (3.44%)	1 (5.88%)	23.56	<0.05*
Upper middle class	2 (50%)	9 (31.03%)	2 (11.76%)		
Middle class	1 (25%)	6 (20.68%)	11 (64.70%)		
Lower middle class	0 (0%)	10 (34.48%)	2 (11.76%)		
Lower class	0 (0%)	3 (10.34%)	1 (5.88%)		
History of feeding within first six months of life					
Exclusive breast feeding	3 (75%)	22 (75.86%)	11 (64.70%)	5.67	>0.05
Top feed only	0 (0%)	2 (6.90%)	0 (0%)		
Combined feeding	1 (25%)	5 (17.24%)	6 (35.30%		
Duration of sun exposure					
1-2 hours	2 (50%)	6 (20.68%)	0 (0%)		
3-4 hours	1 (25%)	9 (31.03%)	10 (71.42%)	21.34	<0.05*
5-6 hours	1 (25%)	13 (44.82%)	3 (17.64%)		
>6 hours	0 (0%)	1 (3.44%)	2 (11.76%)		
No exposure	0 (0%)	0	2 (11.76%)		

The correlation of demographic profile of patients with severity of pneumonia was statistical nonsignificant, which show in table no.2.

Table 2: The correlation of demographic profile of patients with severity of pneumonia

Demographic profile	Severity of pneumonia			$\chi 2$ VALUE	P-value
	No pneumonia (N=8)	Pneumonia (N=23)	Sever pneumonia / Very severe pneumonia (N=19)		
Age (month)					
2-12 months	5 (62.5%)	10 (43.48%)	12 (63.15%)	9.23	>0.05
13-24 months	1 (12.5%)	5 (21.73%)	4 (21.05%)		
25-36 months	1 (12.5%)	4 (17.39%)	1 (5.26%)		
37-48 months	0 (0%)	2 (8.69%)	1 (5.26%)		
49-60 months	1 (12.5%)	2 (8.69%)	1 (5.26%)		
Gender					
Male	6 (75%)	14 (60.87%)	10 (52.63%)	1.58	>0.05
Female	2 (25%)	9 (39.13%)	9 (47.36%)		
Socio economic status					
Upper class	1 (12.5%)	1 (4.34%)	1 (5.26%)	18.28	>0.05
Upper middle class	1 (12.5%)	9 (39.13%)	3 (15.78%)		
Middle class	3 (37.5%)	7 (30.43%)	8 (42.10%)		
Lower middle class	3 (37.5%)	5 (21.73%)	4 (21.05%)		
Lower class	0 (0%)	1 (4.34%)	3 (15.78%)		

Our study showed that in those subjects with sufficient serumVitamin D levels, 50% had no pneumonia while pneumonia and severe pneumoniawas present in only 25% each. In the group with insufficient serum Vitamin Dlevels, 62.06% had pneumonia while 17.24% had severe pneumonia. In the group with deficient serum Vitamin D levels, 64.70% had severe pneumonia while 23.52% had pneumonia. Thus, pneumonia and severe pneumonia was found in increasing frequency in children with insufficient and deficient serum Vitamin D levels which was statistically significant (table 3).

Table 3: Association of serum vitamin d with severity of pneumonia

Vitamin D Levels	No Pneumonia	Pneumonia	Severe Pneumonia Or very Severe Disease	Total	$\chi 2$ VALUE	P-VALUE
Sufficient ≥30ng/ml (N=4)	2 (50%)	1 (25%)	1 (25%)	4		
Insufficient 21-29ng/ml (N=29)	6 (20.68%)	18 (62.06%)	5 (17.24%)	29	38.2	<0.05*
Deficient ≤20ng/ml (N=17)	-	4 (23.52%)	11 (64.70%)	17		
Total	8	23	19	82		

DISCUSSION

Vitamin D has long been known toplay a role in the skeletal system and calcium homeostasis; the deficiency of whichcauses rickets and osteoporosis.[16]There is growing evidence that vitamin D alsocontributes positively to pulmonary health. Clinical vitamin D deficiency (rickets) has been associated with a 13-fold increased risk of pneumonia.[5] Vitamin D deficiency is a common and important nutritional deficiency in children in India. Clinical and subclinical vitamin D deficiency in children has been reported to be a significant riskfactor for severe acute respiratory tract infection.[17] There is evidence to suggest thatsubclinical vitamin D deficiency is common in India despite lying in low latitude and having sunshine in plenty.[8]

WayseVetal[8] observed that subclinical vitamin D deficiency was a significant risk factor for ALRI in children below 5years of age which is in conformity with our study. Rothetal[18] reported similar results in children 1 to 18 months of age who were hospitalized withALRI. In a study comprising of 152 children younger than 59 months of age withpneumonia at Yemen, Vitamin D deficiency was found to be an independent predictor of persistent hypoxemia for children admitted with pneumonia.[19] These studies suggest that Vitamin D deficiency might increase the severity of a respiratory infection in children and that infants and children with vitamin D deficiency andARTI might require higher levels of care than in children with sufficient Vitamin Dlevels.

Overall serum Vitamin D levels were low in the subjects below 5 years of age; however, there was no significant association betweenage and serum Vitamin D levels. High prevalence rates of Vitamin D deficiency are reported in otherwise healthy infants, children and adolescents from India and abroad[1]. Rothetal[18] reported that 25(OH) D levels were significantly lower in children aged 1-18 months with ALRI than in control subjects which is in conformity with our study. In contrast, Way se et al[8] observed a significant increase of serumVitamin D levels with age in children below 5 years with ARTI which is not in conformity with our study.

There was a significant association between socio economic status and serum vitamin D levels in our study. In a review article, it was reported that individuals with hypo vitaminosis D were mostly of low socio-economic status with low daily intake of calcium[52] while another study by Vasudevan Jet al[20] foundthat children from thehigher socio-economic group were at greater risk of hypovitaminosis D probably dueto less sun exposure. However, Wayse Vet al[8] found no relationship between Vitamin D levels and socio- economicstatus ofthechildren with ALRI.

Exclusive breast feeding in the first 4 months of life was significantly associated with decreased risk of severe ALRI in the study conducted by Wayse V etal[8] And Leis Ks et al.[21]On the other hand, Abdul Razzaket al[22] reported that, infants who were exclusively breast fed had a higher risk of Vitamin d deficiency and insufficiency than those who were bottle fed. The vitamin D stores of the newborndepend entirely on the vitamin D stores of the mother. Hence, if the mother is vitaminD-deficient, the infant will be deficient because of decreased mater no-foetal transfer of vitamin D.[23] The risk factors associated with low maternal 25-OHD include loweducational level, insufficient intake of vitamin D in diet and dressing habits.[24] Hence exclusively breast-fed infants may be predisposed to hypovitaminosis D secondary to decreased vitamin D levels in mothers which may in turn predispose the infants toARTI.

The study shows that vitamin D deficiency was significantly more in children receiving less hours of sunlight exposure($p<0.05$*).Cultural and health practices can contribute to vitamin D insufficiency preventing infants from acquiring vitamin D from sun exposure. In some cultures infants are swaddled when outdoors, minimizing their sun exposure.[25] Application of sunscreen lotions and creams to limit the sun's damage to skin can suppress cutaneous

synthesis of vitamin D3 by blocking the absorption of UV B radiation.[10] In addition, atmospheric pollution may decrease the UV rays reaching the children exposed to sunlight in spite of belonging to area with plenty of sunshine as explained in study by Agarwalet al.[26]

CONCLUSION

We conclude that deficiency of vitamin D is a modifiable risk factor in prevention of ARTI. Education regarding the importance of sunlight exposure of young children should be reinforced to mothers and the general community. Also, foods rich in vitamin D-rich should be advocated in order to prevent the morbidity and mortality secondary to ARTI, which globally contribute to morbidity and mortality worldwide.

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