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Original Research Article

Association of serum vitamin D with acute lower respiratory infection in Indian children under 5 years: a case control study

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ABSTRACT

Background: Acute lower respiratory infection (ALRI), primarily pneumonia and bronchiolitis, is a substantial cause of morbidity and mortality in children <5 years of age, particularly in developing countries. Vitamin D deficiency is a significant risk factor for severe ALRI in Indian infants and children <5 years of age. This study was done to determine the relationship, if any, between respiratory illnesses and serum vitamin D status.
Methods: This study included 40 (22 boys and 18 girls) hospitalized children of 6 months to 5 years of age with ALRI as cases and 40 (25 boys and 15 girls) age and sex matched children with no respiratory illness and no clinical manifestation of vitamin D deficiency as controls. Sociodemographic profile, feeding history, immunization history, sun exposure, drug history, causes of admission were taken by interviewing the child's mother or guardian. Serum vitamin D was estimated using commercially available kit by chemiluminiscence technique. General physical and systemic examination with emphasis on respiratory system was performed. ALRI diagnosis was made by clinical, radiographic and biochemical findings.
Results: Among vitamin D deficient and insufficient children, 71% and 74% were adequately exposed to sunlight respectively. 50% vitamin D deficient children were diagnosed of bronchial asthma and 33% of bronchopneumonia. Among vitamin D insufficient, 48% had acute bronchiolitis and 35% had bronchopneumonia. Among sufficient Vitamin D, bronchopneumonia and acute bronchiolitis were 36% each i.e. most of the cases of bronchial asthma (60%) had vitamin D deficiency whereas majority of acute bronchiolitis cases (73%) had vitamin D insufficiency. Statistically significant difference was seen between cases and control among vitamin D sufficient, insufficient and deficient groups with higher number of sufficient vitamin D controls. Low vitamin D levels were significantly correlated with ALRI.
Conclusions: Subclinical vitamin D deficiency is significant risk factors for severe ALRI in Indian children of less than 5 years of age.

Keywords: ALRI, Sunlight exposure, Vitamin D

INTRODUCTION

Acute lower respiratory infection (ALRI), primarily pneumonia and bronchiolitis, is a substantial cause of morbidity and mortality in children younger than 5 years of age, particularly in developing countries. Worldwide, 20% mortality among children aged less than 5 years is attributed to respiratory tract infections (predominantly pneumonia associated). With neonatal pneumonia inclusive, 35-40% mortality among children aged less than 5 years account for 2.04 million deaths/year. Southeast Asia stands first in number for ARI incidence accounting for more than 80% of all incidences together with sub Saharan African countries.[1,2] In India, more than

4 lakh deaths every year are due to pneumonia accounting for 13%-16% of all deaths in the pediatric hospital admissions.[3,4] Pneumonia related mortality is maximum in central India.[5] Recent estimates suggest 3.5% of the global burden of disease is caused by ARI.[6] Recent community based estimates from prospective studies report that 70% of the childhood morbidities among children aged less than 5 years are due to ARI.[7]

Besides low birth weight, nonexclusive breastfeeding, incomplete immunization, indoor air pollution, passive smoking, and chronic disease, reduction of ultraviolet-B radiation exposure during winter is hypothesized to be associated with decreased vitamin D production that could account partly for the increased prevalence of ALRI during winters.[8,9] Vitamin D deficiency is known to cause rickets and retarded skeletal growth. Studies in developing countries have suggested an association between nutritional rickets and pneumonia. 43% of 200 children with rickets in Iran and 44% of 250 in Kuwait had radiologically proven pneumonia.[10,11] A hospital based case control study from Egypt showed that ALRI were present in 81% of children with rickets as compared to 58% of controls.[12] In a hospital based study of 300 inpatients of less than 5 years of age in Ethiopia, rickets was associated with 13-fold increased risk of pneumonia.[13,14] Subclinical vitamin D deficiency is a significant risk factor for severe ALRI in Indian children less than five years of age.[15] Low serum vitamin D levels are related to increased incidence of respiratory infections and respiratory syncytial virus disease in infants and children less than 5 years age.[15-18] Such research is important given the increasing evidence that subclinical vitamin D deficiency is common even in countries at low latitude and with plentiful sunshine, including India and Pakistan.[19-21]

In India, a little work has been done to investigate status of vitamin D in various childhood respiratory illnesses. Hence, to address this issue, we aimed to compare serum vitamin D status of children (6 months to 5 years) suffering from various types of ALRI with those having no respiratory illness so as to find out relationship, if any, between respiratory illnesses and serum vitamin D status.

METHODS

The present study was a case control study conducted on 80 children from 6 months to 5 years of age admitted or attending OPD in department of Pediatrics, JLN Medical College, Ajmer from April 2013 to March 2014. The Case group comprised of children admitted with respiratory illnesses like pneumonia, acute bronchiolitis, asthma. Controls were children who were receiving care at the Hospital's ambulatory, emergency or in-patient units and presenting with non-respiratory complaints and not having any clinical manifestation of vitamin D deficiency. Controls were matched as per age, sex and nutritional status. Children with chronic renal disease, on drugs affecting vitamin D metabolism (eg. Phenobarbitone, Phenytoin, sodium valproate) and corticosteroids were excluded from the study. None of the mothers of cases reported vitamin D supplementation to the child. Institutional ethical clearance was obtained for the study. Written consent was taken from parents of children before they were subjected to full medical history (from parents) and clinical examination. Socio demographic profile, feeding history, immunization history, sun exposure, drug history was taken.

Clinical evaluation (including anthropometry), general physical and systemic examination with emphasis on respiratory system examination was performed. The ALRI diagnosis was made by clinical, radiographic and biochemical findings. Weight was measured using electronic weighing scale accurate to 5 gms (PHOENIX, Nitiraj Eng. Private Ltd.). Ideal weight for age was taken as per WHO multicentric growth reference study.[22] Length of child was measured up to nearest centimeter using infantometer (ADE, Germany) up to 2 years of age and height was measured using stadiometer after 2 years of age. Body mass index was calculated. Vitamin D was estimated using commercially available kit (Siemens Advia Centaur) by chemiluminiscence technique (CLIA).

Criteria for adequacy of sun exposure were taken as given by Specker et al according to which exposure for 30 min/wk for infants in diaper and 2 hours/week for fully clothed infant without cap (since infant scalp contributes major part of body surface area) maintained vitamin D level of >11 ng/dL. Since Asian children require three times of sun light exposure due to dark skin color, so we took sun exposure of 90 min/wk for infants in diaper and 6 hour/wk for fully clothed infant as adequate.[23]

All the above mentioned information was recorded on pre structured Performa and tabulated in a concise and logical order to provide basis for statistical computation. Data were recorded in a computerized database and analyzed using statistical software SPSS (Version 19.0; SPSS Inc., USA). Standard statistical tests were used to calculate Z-score and P value. A z-score value of 1.98 or more was considered significant at 0.05 level of significance ($p = 0.05$) and z- score value of more than 2.60 was considered significant at 0.01 level of significance ($p = 0.01$). For study purpose p value of <0.05 was considered significant.

RESULTS

More than half of the study population fell into the age group of 1 to 2 years. 22 boys and 18 girls constituted the 40 cases while 25 boys and 15 girls were enrolled as 40 controls in our study. In all there were 59% boys and 41% girls.

Table 1: Serum vitamin D status in relation to rural and urban population.

	Deficiency (n = 7)		Insufficiency (n = 31)		Sufficient (n = 42)		Total (n = 80)
	Case and control		Case and control		Case and control		
Rural	2 (28.56%)		13 (41.93%)		18 (42.85%)		33 (41.25%)
Urban	5 (71.44%)		18 (58.06%)		24 (57.14%)		47 (58.75%)
Total	7		31		42		80
Rural Vs Urban	Z score	P value	Z score	P value	Z score	P value	
	1.77	>0.05	1.29	>0.05	1.32	>0.05	

Statistically no significant difference was seen in rural or urban children regarding vitamin D status.

Table 2: Breast feeding status of cases and controls.

Breast feeding status	Case (n = 34)	Control (n = 32)	Total (n = 66)
Exclusive breast fed up to 4 months	8 (23.5%)	7 (21.8%)	15 (22.7%)
Exclusive breast fed up to 6 months	10 (29.4%)	11 (34.3%)	21 (31.8%)
Partial breast fed	12 (35.2%)	13 (40.6%)	25 (37.8%)
Never breast fed	4 (11.7%)	1 (3.1%)	5 (7.5%)
Total	34	32	66

Due to paucity of data collected for breast feeding history, correlation of breast feeding status with serum vitamin D could not be studied.

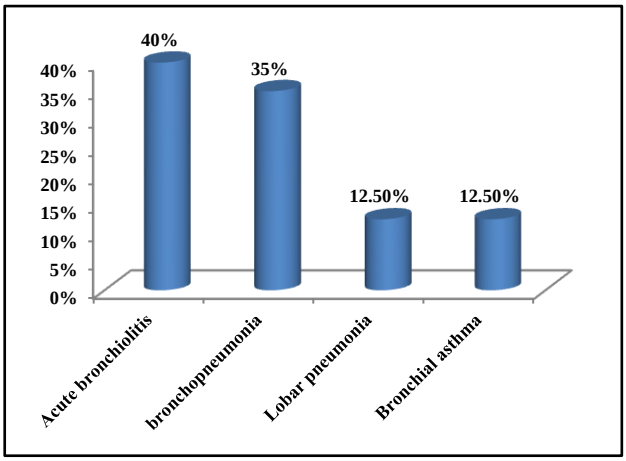

Figure 1: Distribution of cases as per diagnosis.

Table 3: Sun exposure adequacy and vitamin d status of subjects.

Sun exposure	Deficiency (n = 7)		Insufficiency (n = 31)		Sufficiency (n = 42)		Total (n = 80)
	Cases and controls		Cases and control		Cases and controls		
Adequate sun exposure	5 (71.42%)		23 (74.19%)		32 (76.19%)		62 (77.5%)
Inadequate sun exposure	2 (28.57%)		8 (25.80%)		10 (23.8%)		18 (22.5%)
Total	**7**		**31**		**42**		**80**
Adequate versus Inadequate sun exposure	Z score	P value	Z score	P value	Z score	P value	
	1.77	>0.05	4.35	<0.05	6.38	>0.05	

Table 4: Serum vitamin d status of cases and controls.

	Deficiency (n = 7)		Insufficiency (n = 31)		Sufficient (n = 42)		Total (n = 80)
Cases	6 (85.71%)		23 (74.19%)		11 (26.19%)		40
Controls	1 (14.28%)		8 (25.80%)		31 (73.80%)		40
Total	**7**		**31**		**42**		**80**
Cases versus controls	Z score	P value	Z score	P value	Z score	P value	
	3.82	<0.05	4.35	<0.05	4.96	<0.05	

Statistically significant difference was seen between cases and control among all the three vitamin D status groups with higher number of controls having sufficient vitamin D levels.

In vitamin D deficient children, bronchial asthma and bronchopneumonia cases were 50% and 33% respectively. Among vitamin D insufficient children 48% had acute bronchiolitis and 35% had bronchopneumonia. In children with sufficient Vitamin D, bronchopneumonia and acute bronchiolitis were 36% each. Difference in vitamin D levels in pneumonia and Wheeze associated respiratory illnesses (WARI) was statistically insignificant.

DISCUSSION

The objective of our study was to find out relationship, if any, between respiratory illnesses and serum vitamin D status in children of 6 months to 5 years of age.

All the subjects of our study were <5 years of age. Our study was similar to several other studies like that of Wyase et al, Gordon et al, Lubani MM et al, Banajeh SM et al who included children of <5 years of age.[11,15,24,25] We focused on this age group because ALRI are leading cause of Under 5 mortality (U5MR) in India. According to WHO report (2007) ALRI contributes to 19% deaths in under 5 mortality.[2] Acute bronchiolitis is seen commonly in children below 2 years of age whereas bronchial asthma is seen in older age group.

As per census 2011, sex ratio of Ajmer is 951 females per 1000 males which reflected in our study as a sex ratio of M:F = 3:2.[26] Similar sex distribution was observed in studies by V Wayse et al.[15]

Majority (64%) of children in our study fell into grade II and III nutritional status and 15% into grade III and IV. It shows that Protein Energy Malnutrition is associated co-morbidity in cases of ALRI. As per NFHS-3 (2005-2006) reports, 44% children are undernourished while as per Human development report by Government of Rajasthan, 54% is prevalence of malnutrition.[27] Higher incidence of malnutrition in our study may be due to occurrence of ALRI as a co morbid feature leading to hospital admission. Being tertiary level hospital, critically ill children are referred from periphery, so a higher incidence of malnutrition is reflected. The difference between vitamin D deficiency and insufficiency in children with mild to moderate malnutrition and children with normal nutritional status was statistically significant. Majority (57%) of vitamin D deficiency was seen mainly in children from Class IV and V SE status. Number of children in vitamin D insufficient and sufficient group belonging to class II+III SE status were 67% and 57% respectively. 67% of grade III+IV malnourished children showed hypovitaminosis D.

Data about breastfeeding could be collected for total 66 children (34 cases and 32 controls). Of these, 31.8 % were exclusively breastfed up to 6 months, 22.7% up to 4 months and 37.8% had both mother feed and top feeding since birth. Since, data regarding breast feeding were not available for all the subjects; serum vitamin D status in relation to breastfeeding status could not be studied.

Among the vitamin D deficient and insufficient children 71% and 74% were adequately exposed to sunlight respectively. Presence of low vitamin D level in large number (45%) of subjects with adequate sun exposure indicates that only sun exposure cannot be attributed as sole factor in vitamin D synthesis. Skin color, level of pollution in environment, covering of body during sun exposure, sunscreen application is to be considered as these factors influences the vitamin D synthesis subcutaneously.[28] The age old Indian practice of oil massaging in sunlight indirectly helps in subcutaneous vitamin D synthesis needs to be promoted. Ahmed P et al (2015) in Nigeria found that only lower percentage of body surface area exposed to sunlight was associated with increased risk of ALRTI.[29]

In current study, 47.5% cases were diagnosed of Pneumonia (35% Bronchopneumonia and 12.5% Lobar pneumonia) and 52.5% (40% Acute bronchiolitis and 12.5% bronchial asthma) cases belonged to WARI category. Ahmed P et al in Nigeria found an association of ALRTI with less exposure to sunlight rather than vitamin D status.[29] Similarly, McNally JD et al found no significant difference in vitamin D levels between the entire ALRI group and control groups.[30]

Our study had a preponderance of cases (86% and 74%) in vitamin D deficiency and insufficiency group respectively. The main finding of the study was that serum Vitamin D concentrations in children with ALRI (study group) were lower than those with no ALRI (control group). A total of 47.5% cases showed hypovitaminosis D as compared to only 22.5% controls. This difference was statistically significant. It reflects role of hypovitaminosis D in occurrence of respiratory diseases in children. Quite similar results were observed by Gordon et al.[24] On the contrary, McNally JD et al found no significant difference in vitamin D levels between the entire ALRI group and control groups; however, significantly more children admitted to the pediatric ICU with ALRI were vitamin D deficient. These findings suggest that the immunomodulatory properties of vitamin D might influence ALRI disease severity.[30]

50% vitamin D deficient children were diagnosed of bronchial asthma and 33% of bronchopneumonia. Among vitamin D insufficient, 48% had acute bronchiolitis and 35% had bronchopneumonia. In sufficient Vitamin D children, bronchopneumonia and acute bronchiolitis were 36 % each. So it appears that most of the cases of bronchial asthma (60%) had vitamin D deficiency whereas majority of acute bronchiolitis cases (73%) had vitamin D insufficiency. Our results were consistent with Bener A, et al who found that 53% cases of asthma had serum vitamin D levels < 20 nmols/L.[28] Chinellato et al found that vitamin D deficiency and insufficiency was present in 51% and 37% cases respectively which was

higher than our study.[31] The probable explanation of the above findings could be that airway epithelial cells can hydroxylate 25(OH)D to its active form ($1,25(OH)_2D_3$), leading to increased differentiation and recruitment of macrophages, enhanced production of cathelicidin and CD14 and potentiation of host defenses against bacteria, fungi, and viruses.[32-34] Vitamin D may influence asthma by regulating the expression of disease-susceptibility genes and through modulation of T regulatory cells (Tregs).[35] Vitamin D has also been shown to increase serum levels of the immune-modulatory cytokines through vitamin D Receptors (VDRs).[36] Low vitamin D level is associated with impaired lung function in asthmatic children, thus lower serum vitamin D levels are a contributory factor in bronchial asthma. Due to our smaller sample size, we could not establish a significant difference in relation of vitamin D levels with pneumonia and WARI.

CONCLUSION

Our study emphasizes the need for serum vitamin D estimation in various respiratory illnesses even in face of protein energy malnutrition so that appropriate and timely therapeutic intervention can be initiated to decrease morbidity and mortality in under five children.

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REFERENCES

1. Wardlaw TM, Johansson EW, Hodge MJ. UNICEF; 2006. World Health Organization. Pneumonia: The Forgotten killer of Children. Available at: http://www.who.int /maternal_child_adolescent /documents / 9280640489/en. Accessed on 25 July, 2016.
2. UNICEF; 2008. The State of Asia Pacific's Children 2008: Child Survival. Available at: http: //www.unicef.org/sapc08/report/report.php. Accessed on 25 July, 2016.
3. Jain N, Lodha R, Kabra SK. Upper respiratory tract infections. Indian J Pediatr. 2001;68:1135-8.
4. Vashishtha VM. Current status of tuberculosis and acute respiratory infections in India: Much more needs to be done! Indian Pediatr. 2010;47:88-9.
5. Causes of neonatal and child mortality in India: A nationally representative mortality survey Causes of neonatal and child mortality in India 2010. Available at: http://cghr.org/wordpress/wpcontent/ uploads/ Causes of neonatal and child mortality in India 2010. Pdf. Accessed on 25 July, 2016.
6. Rudan I, Boschi Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008;86:408-16.
7. Dongre AR, Deshmukh PR, Garg BS. Health expenditure and care seeking on acute child morbidities in periurban Wardha: A prospective study. Indian J Pediatr. 2010;77:503-7.
8. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008;86:408-16.
9. Cannell JJ, Vieth R, Umhau JC. Epidemic influenza and vitamin D. Epidemiol Infect. 2006;134:1129-40.
10. Salimpour R. Rickets in Tehran. Arch Dis Child. 1975;50:63-5.
11. Lubani MM, Al-Sheb TS, Sharda DC, Quattawi SA. Vitamin-D deficiency rickets in Kuwait: the prevalence of preventable disease. Ann Trop Paediatr. 1989;3:134-9.
12. Lawson DEM, Cole TJ, Salem SI. Aetiology of rickets in Ethiopian children. Hum Nutr Clin Nutr. 1987;41:199-208.
13. Auss-Kettis A, Bjornesjo KB, Manneimer E, Cvibach T. The occurrence and clinical picture of disease in a clinic in Addis Ababa. Ethiopia Med J. 1965;3:109-21.
14. Muhe L, Lulseged S, Mason KE, Simoes EAF. Case control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. Lancet. 1997;349:1801-4.
15. Wayse V, Yousafzai A, Mogale K, Filteau S. Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 years. Eur J Clin Nutr. 2004;58:563-7.
16. Roth DE, Shah R, Black RE. Vitamin D status and acute respiratory infection in early childhood in sylhet, Bangladesh. Acta Paediatr. 2010;99:389-93.
17. Inamo Y, Hasegawa M, Saito K. Serum vitamin D concentrations and associated severity of acute respiratory infection in Japanese hospitalized children. Pediatr Int. 2011;53:199-201.
18. Belderbos ME, Houben ML, Wilbrink B. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics. 2011;127:1513-20.
19. Atiq M, Suria A,Nizami SQ, Ahmed I. Vitamin D status of breastfed Pakistani infants. Acta Pediatr. 1998;87:737-40.
20. Goswami R, Gupta N, Goswami D, Marwaha RK. Prevalence and significance of low 25-hydroxyvitamin D concentration in healthy subjects in Delhi. Am J Clin Nutr. 2000;72:472-5.
21. Andran N, Yordam N, Ozon A. Risk factor for vitamin D deficiency in breastfed new-borns and their mothers. Nutrition. 2002;18:47-50.

22. WHO child growth standards. Acta pediatr supplement. 2006;450:5-101.
23. Specker BL, Valanis B, Hertzberg V, Edwards N. Sunshine exposure and serum 25 hydroxyvitamin D concentrations in exclusively breastfed infants. J Pediatr. 1985;107(3):3726.
24. Gordon CM, Feldman HA, Sinclair L, Williams AL. Prevalence of vitamin D deficiency among healthy infants and toddlers. Arch Pediatr Adolesc Med. 2008;162(6):505-12.
25. Banajeh SM, Al-Sunbali NN, Al-Sanhani. Clinical characteristics and outcome of children aged under 5 years hospitalized with severe pneumonia in Yemen. Ann Trop Paediatr. 2007;17:321-6.
26. Census data 2011. Available at http://censusindia.gov.in/2011-prov-results/paper2 /data_files /india / Rural_ Urban _2011.pdf. Accessed on 25 July, 2016.
27. Human development report, Government of Rajasthan. 2008. Available at http://www.in.undp.org/content/dam/india/docs/rajasthan_factsheet.pdf. Accessed on 25 July, 2016.
28. Bener A, Al-Ali M, Hoffmann GF. Vitamin D deficiency in healthy children in a sunny country: associated factors. Int J Food Sci Nutr. 2009;60(5):6070.
29. Ahmed P, Babaniyi IB, Yusuf KK, Dodd C. Vitamin D status and hospitalisation for childhood acute lower respiratory tract infections in Nigeria. Paediatr Int Child Health. 2015;35(2):151-6.
30. McNally JD, Leis K, Matheson LA, Karuananyake C. Vitamin D deficiency in young children with severe acute lower respiratory infection. Pediatr Pulmonol. 2009;44(10):9818.
31. Chinellato I, Piazza M, Sandri M, Peroni D. Vitamin D serum levels and markers of asthma control in Italian children. J Pediatr. 2011;158:437-41.
32. Joseph N, Unnikrishnan B, Naik VA, Mahantshetti NS. Infant rearing practices in South India: a longitudinal study. J Family Med Prim Care. 2013;2(1):3743.
33. Darmstadt GL, Saha SK. Traditional practice of oil massage of neonates in Bangladesh. J Health Popul Nutr. 2002;20(2):1848.
34. Hansdottir S, Monick MM, Lovan N, Powers L. Vitamin D decreases respiratory syncytial virus induction of NF-kappa B-linked chemokines and cytokines in airway epithelium while maintaining the antiviral state. J Immunol. 2010;184:965-74.
35. Hawrylowicz CM, O'Garra A. Potential role of interleukin-10 secreting regulatory T cells in allergy and asthma. Nat Rev Immunol. 2005;5:271-83.
36. Sutherland ER, Goleva E, Jackson LP. Vitamin D levels, lung function, and steroid response in adult asthma. Am J Respir Crit Care Med. 2010;181:699-704.

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