Cohort study showing correlation of Vitamin D levels with severity of illness in children admitted with acute febrile illness

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ABSTRACT

Background: Acute febrile illness (AFI) which is characterized by illness without any identified source has been less explored. However, no studies have correlated AFI, its various etiologies along with stay in hospital duration, and admission in paediatric intensive care unit (PICU) with Vitamin D levels as per our knowledge. **Objective:** The present study was conducted with a cohort of children having Vitamin D deficiency (VDD) and individuals with adequate levels of Vitamin D and a correlation among them was tried to be established. **Materials and Methods:** We conducted this study at the pediatric department of a tertiary hospital of Western India using the standard protocol. We determined severity of illness using six observational items and their scales as per acute illness observation scale (AIOS). Laboratory investigations such as complete hemogram, renal function tests, liver function tests, bacteriology cultures, radiography, and sonography were done as per indication. Serum calcium, serum phosphorous, and serum alkaline phosphatase levels were evaluated in all patients. Evaluation of Vitamin D status was done in all children within 48 h of admission to the hospital using chemiluminescent immunoassay method. Outcome parameters such as the duration of hospital stay and final outcome as discharged or death were noted. **Results:** We found bronchiolitis as the major etiology in most of the AFI cases. The children which required NICU admission had VDD. Children, who had AIOS score >10, indicating that severity of disease was also maximum from VDD group. Moreover, the hospital stay of VDD group was significantly higher. **Conclusion:** Overall data suggested that condition of children with AFI deteriorated more in the group which are deficient in Vitamin D suggesting that supplementation of Vitamin D could be fruitful strategy to reduce the disease severity.

Key words: Febrile illness, Hospitalized children, Vit.D Deficiency

Vitamin D is a hormone responsible for maintaining the bone density. Thus, the role of Vitamin D as immunomodulator effecting both arms of immunity, namely, on the innate and adaptive immune system, which modulate the expression of antimicrobial peptides and thereby modulating the inflammatory signaling pathway by involving nuclear factor kappa B has been recognized [1]. Various studies have been conducted establishing the association of Vitamin D with respiratory diseases [2].

A study was conducted for 2 years in pediatric patients of tuberculosis (TB) in the United Kingdom and it was found that more than 80% of patients were deficient for Vitamin D. Other studies across the world also showed similar outcomes [3]. Along with TB, the risk for gastroenteritis has also been found to be related to Vitamin D deficiency (VDD) [4]. A study indicated that Vitamin D might be correlated to bacterial infections such as *Salmonella* or *Shigella* [5].

Malarial infection has also been found to be linked to VDD in children within the age group of 1.4–12 years [6] and animal model of *Plasmodium berghei* infection of cerebral malaria also showed inhibition of infection after Vitamin D supplementation along with antimalarial drugs [7].

Infectious diseases such as childhood diarrhea, acute respiratory tract infections, and vaccine preventable diseases including TB besides malnutrition are major causes of under-five mortality in India [8]. There could be an implication of newly recognized role of Vitamin D in immune regulation and control of such infectious illnesses [9,10].

Acute febrile illness (AFI) which is characterized by illness without any identified source is less characterized in various parts of world [11]. Various infections such as salmonella, typhoid, and brucellosis were found be a cause of AFI [12] along with malaria, dengue, childhood diarrhea, acute respiratory tract infections, and vaccine preventable diseases including TB [13,14]. The purpose of the present study was to evaluate Vitamin D (25(OH)D) status in children presenting with AFI and required hospitalization and correlate it with severity of illness.

MATERIALS AND METHODS

This study was conducted at the pediatric department of a tertiary hospital of Western India using proper protocol and ethical

clearance from the Institutional Ethics Committee. The sampling was done based on universal sampling method. We included children within the age range of 1 month–12 years, admitted for over 6 months with AFI with or without clinical or biochemical parameters showing rickets. AFI symptoms included increase in body temperature by more than 37.5°C due to any infection. We excluded children above 12 years or younger than 1 month or showing any disorder which could affect the metabolism of Vitamin D such as chronic liver disease, chronic kidney disease, prolonged medications such as anticonvulsants, protein kinase B or AKT and those who received Vitamin D supplementation along with those who were directly admitted to pediatric intensive care unit (PICU).

The patient's history was recorded in a predesigned pro forma of the hospital along with the data such as gestational age at birth, birth weight, and any perinatal events. Various other parameters such as dietary intake of Vitamin D as well as exposure time to sun, its duration along with body parts being exposed was also recorded. Thorough examination of children was done to evaluate anthropometric parameters such as weight, height, and circumference of head. The illness for which the child was admitted was also thoroughly evaluated. All the vital parameters, along with stigmata of nutritional deficiency states including pallor and signs of other vitamin deficiency, were also examined. Children were also assessed for symptoms and signs of rickets.

Severity of illness was determined using six observational items and their scales as per acute illness observation scale (AIOS) that is used widely and reliably to identify serious illness in febrile children with validation [15]. According to this scale, normal finding is scored as 1, a moderate impairment as 3, and severe impairment as 5. Assessment of all the six parameters would give a best possible score of 6 (6 items×1=6), whereas the poorest score suggesting serious illness would be 30 (6 items×5=30). According to AIOS, the chance of serious illness is 1–2% if the total score is 10 or less and the risk of serious illness increases by at least 10-fold if the score >10.

In our study, mild illness was defined as AIOS ≤10; while moderate-to-severe illness was defined as AIOS >10. Laboratory investigations such as complete hemogram, renal function tests, liver function tests (rule out liver or kidney diseases), bacteriology cultures, radiography, and sonography were done as per indication. Serum calcium, serum phosphorous, and serum alkaline phosphatase levels were evaluated using automated ERBACEN 5+ biochemistry machine. Evaluation of Vitamin D status was done in all children within 48 h of admission to the hospital using early morning sample of 2 ml of serum using chemiluminescent immunoassay method.

Treatment given for underlying disease in the form of need of oxygen, parenteral fluids, and antibiotic therapy, any other medications such as nebulization therapy, anticonvulsants, inotrope required, and requirement of PICU care were recorded. Children found to be deficient or insufficient in Vitamin D were treated with cholecalciferol (Inj. Arachitol®) given orally to all these children as per unit protocol. All the children including those who had sufficient 25(OH)D levels were advised to take a daily maintenance dose of 400 units of cholecalciferol. The outcome parameters such as the duration of hospital stay and final outcome as discharged or death were noted.

RESULTS

Of the 90 children enrolled in the study, demographic characteristics are mentioned in Table 1. In this series, the mean 25(OH) D level was 17.53±15.48 ng/ml. Out of the 90 children in this cohort, VDD (25(OH)D <10 ng/ml) was seen in 37 (41.1%) children, whereas 35 (38.9%) had Vitamin D insufficiency (25(OH)D between 10 and 30 ng/ml and only 18 (20%) had Vitamin D sufficiency (25(OH)D >30 ng/ml) (Table 1).

Respiratory illness in the form of bronchiolitis was the most common etiological diagnosis (n=22/90; 24.4%) of AFI (Table 2).

In our study, respiratory system affection was the most common etiology seen in 36% of cases, whereas central nervous system affection was found in 25% of cases (Table 2).

Based on the AIOS, 75.6% (n=68/90) of children had moderate-to-severe illness. We found that children in AIOS group >10 were significantly higher when compared with AIOS<10. Moreover, in the group AIOS >10, more than 82% of children were VDD suggesting a strong correlation between AFI and VDD (Table 3).

Intensive care in PICU was required at some point of the course in ward in 8 (9%) children and 6 (75%) of them were VDD. None of the 18 (20%) children who had Vitamin D sufficiency needed PICU care. The need for intensive care decreased as the 25(OH) D levels improved although this correlation was not statistically significant.

During the hospital stay, 5 (5.6%) children required cardiovascular support with inotrope and of which 4 (80%)

Table 1: Demographic characteristics

Parameter	Frequency (n=90)	Percentage	Mean	SD
Age (year)			1.85	2.74
<1	45	50.0		
≥1	45	50.0		
Gestational age at birth				
Full term	86	95.6		
Preterm	4	4.4		
Sex				
Female	26	28.9		
Male	64	71.1		
Birth weight (kg)			2.73	0.49
<2.5	18	20.0		
≥2.5	72	80.0		
Socioeconomic class				
Lower middle	20	22.2		
Upper lower	1	1.1		
Upper middle	61	67.8		
Upper	8	8.9		

were VDD. None of the children with Vitamin D sufficiency needed inotrope. However, the correlation was not statistically significant. The mean duration of hospital stay in the study cohort was 8.73±6.83 days, (minimum: 3 days; maximum: 40 days). All children in this cohort were discharged and there were no deaths. We found that VDD group had significantly a longer duration hospital stay as compared to group with sufficient Vitamin D levels (p=0.0024) (Table 4).

DISCUSSION

In our series of 90 children enrolled, the mean S.25 (OH) Vitamin D level was 17.53±15.48 ng/ml. Only 20% of children (n=18/90) in this cohort were Vitamin D sufficient and 80% were either VDD or Vitamin D insufficient. The data suggest that there is high incidence of VDD/insufficiency in this cohort of Indian children which has been shown by other Indian studies also. Seth *et al*. found a high prevalence of VDD in lactating mothers and their exclusively breastfed infants [16]. In a large school-based study of girls from Delhi, biochemical VDD was found in 90.8% of girls [17].

The etiology of AFI in this group was predominantly due to respiratory tract infection (bronchiolitis, pneumonia, and lung abscess) seen in 33 (36.6%) children. The other etiologies included affection of central nervous system (pyogenic meningitis, tuberculous meningitis, and febrile convulsion) in 26.6% of cases and other etiologies in the remaining 33 cases.

Upper respiratory tract infections (URTIs), or common colds, are the most widespread of infectious diseases, with more than 200 viruses contributing to the clinical symptoms. Early epidemiological studies found a strong association between rickets and RTI, and a recent large cross-sectional study reported that Vitamin D status is associated inversely with recurrent URTI and that the association may be stronger in those with respiratory diseases, such as asthma [18]. There are strong evidences suggesting that consumption of Vitamin D could reduce the susceptibility of children toward RTI. Initially, this was correlated only with TB [19].

In another study, Camargo *et al*. found that Vitamin D supplementation decreased the risk of RTI among children who had low blood levels Vitamin D at the start of the study [20]. Supplementation with Vitamin D has been shown to slash the risk of winter time RTI by half [20].

Severity of illness graded as mild or moderate to severe, based on AIOS score showed that 68 (75%) children had a AIOS score of >10 depicting moderate to severe illness and 82% of them were either VDD. In a study of 100 intensive care unit patients, by a group of endocrinologists in Sydney [21], correlating the Vitamin D levels with a disease severity score, it was found that VDD had a strong correlation with adverse outcomes in such patients. Various other observational studies have shown association between the deficiency of Vitamin D and adverse outcomes of the disease [22,23].

Systematic review compiling 14 observational studies with 9715 critically ill patients showed association between sepsis and risk of death and it was found that VDD had a strong

Table 2: Etiological diagnosis of acute febrile illness

Diagnosis	No. of patients
Bronchiolitis	22
Febrile convulsion	15
Pneumonia/lung abscess	9
Dengue fever	7
Pyogenic meningitis	5
TB meningitis/miliary TB	3
Sepsis	5
Acute gastroenteritis	4
Nephrotic syndrome with febrile illness (SBP, URTI, and UTI)	4
Viral febrile illness	5
Malaria	2
UTI	2
Liver abscess	1
Tonsillitis	1
Pyomyositis	1
VSD with LRTI	1
Scrub typhus	1
NOMID (Neonatal onset multisystem inflammatory disorder)	1
Ectodermal dysplasia with bacterial sepsis.	1

Table 3: Vitamin D distribution stratified by severity of AFI, need of NICU, cardiovascular support, and duration of hospital stay

Vitamin D status	AIOS >10 ^^(n=68) N(P)	AIOS ≤10 ^(n=22) N(P)	Need of NICU admission (n=8) N(P)	Need of cardiovascular support (n=5) N(P)
Deficient# (n=69)	56(82.35%)	13(59.09)	8 (11.59%)	5(7.25%)
Sufficient## (n=21)	12(17.65 %)	9 (40.9)	0	0
p	0.025		0.1	0.2

#Vit D levels ≤30 ng/ml, ##Vit D levels >30 ng/ml, AIOS: Acute illness observation scale, ^^: moderate-to-severe illness, ^: mild illness, NICU: Neonatal intensive care unit

Table 4: Duration of hospital stay stratified by status of Vitamin D and severity of AFI

Duration of hospital stay	AIOS >10 ^^(n=68)	AIOS ≤10 ^(n=22)	Vit. D deficient# (n=69)	Vit. D sufficient## (n=21)
Mean±SD (Days)	9.57±7.32	6.14±4.18	9.49±6	5.33 ±1.72
p	0.0075		0.0024	

#: Vit D levels ≤30 ng/ml, ##: Vit D levels >30 ng/ml, AIOS: Acute illness observation scale, ^^: Moderate-to-severe illness, ^: Mild illness

association with increased risk of severe infection and death [24]. One systematic review covering PICU population showed 50% prevalence of VDD at the time of admission [25]. In our series, eight of children admitted, required intensive care. The PICU care was required during the course of ward stay and not on arrival.

Ventilatory care, need for inotropes was analyzed in this group of children. It was found that five children needed inotrope support. McNally *et al*. [26] conducted a prospective cohort study, from 2005 to 2008 in six tertiary care PICUs in Canada, and examined data from 326 children and teens (median age 3.7 years). The prevalence of 25(OH)D<50 nmol/L was 69% and 23% for levels between 50 and 75 nmol/L. Lower levels of 25(OH)D were associated with hypocalcemia, catecholamine utilization, and need for significant fluid bolus administration. VDD was also independently associated with a longer PICU length of stay (+1.92 days, p=0.03) and increasing severity of illness as determined by the pediatric risk of mortality score with every additional point increasing the likelihood of being VDD by 8% (p=0.005). In our series, none of the children with sufficient 25(OH)D levels needed PICU care. Graham *et al*. did a study to find out incidence of VDD in neonates with congenital heart disease and found that lower post-operative 25(OH)D levels were associated with the need for increased inotropic support in neonates undergoing cardiac operations [27].

In our study, out of five children requiring inotrope support, 4 (80%) of them had 25(OH) D levels <10 ng/ml, while one child had Vitamin D insufficiency. Here again, none of the children from Vitamin D sufficient group needed inotrope support. This may be due to the effect of Vitamin D on myocardial contractility or due to associated hypocalcemia or hypophosphatemia. Correlation of the need of inotrope in VDD states had been shown in other studies also [27].

In our cohort, the duration of hospital stay in children with sufficient 25(OH)D levels was significantly less than those children with deficient levels of Vitamin D. Similar results have been shown in other studies as Youssef *et al*. found that the total length of hospital stay was 4 times greater in the VDD group [28]. As infections form a common cause of mortality in young infants and children in our country, and VDD is associated with infective conditions, a larger population-based prospective study of Vitamin D status and under-five mortality due to infections can validate these results. The study had a few limitations. The sample size was small and the study period was short.

CONCLUSION

Overall data suggested that condition of children with AFI deteriorated more in the group which are deficient in Vitamin D, suggesting that supplementation of Vitamin D could be fruitful strategy to reduce the disease severity.

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