

Vitamin D Status in Neonatal Pulmonary Infections: Relationship to Inflammatory Indicators

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Abstract

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AIM: The study aimed to evaluate serum vitamin D concentrations among neonates with pneumonia.

METHODS: This case-control study enrolled 33 neonates with pneumonia in addition to 30 healthy controls. CBC, CRP, Serum vitamin D and Pentraxin 3 levels were measured for all participants.

RESULTS: There was significant difference between patients and controls regarding Hemoglobin levels, TLC and CRP (p value < 0.01, = 0.002, < 0.01 respectively). Patients with pneumonia showed significant lower levels of Vit. D (9 ± 2.1) compared to controls (14.1 ± 2.8), P value < 0.01. However, patient group had significant higher levels of Pentraxin 3 (29.1 ± 4.8) compared with controls (12.6 ± 3), P value < 0.01. Moreover, mechanically ventilated patients revealed significant lower vit D (7.7 ± 1.8) and higher pentraxin 3 (32.2 ± 2.6) compared to patients on free oxygen (9.1 ± 2.1 , 26.4 ± 3.7 respectively), P value = 0.05, 0.02 respectively. Regarding hospital stay, it had significant positive correlation with serum pentraxin 3 (r = 0.6, P value < 0.01) and significant negative correlation with serum vit D (r = -0.4, P value = 0.04). Finally a significant negative correlation between serum levels of vitamin D and Pentraxin 3 was found (r = -0.4, P value = 0.01).

CONCLUSION: Lower concentration of serum vitamin D may be significantly associated with neonatal pneumonia. It also can predict the need for mechanical ventilation and duration of hospital stay in neonatal pneumonia. Similarly, higher levels of Pentraxin 3 may be used as an indicator for mechanical ventilation need and a longer hospital stay in neonates with pneumonia.

Introduction

Pneumonia is broadly defined as lung inflammation induced by an infectious agent who stimulates a response resulting in lung tissue damage [1]. Globally pneumonia accounts for nearly one in five deaths among children > 5 years of age [2]. Etiological factors for pneumonia vary according to age, source of infection (community or hospital-acquired pneumonia) and underlying host defects as immunodeficiency [3]. In neonatal periods, the underdeveloped immune system predisposes newborns, especially preterm to pulmonary infections, which is a major cause of death [4].

Vitamin D is a steroid hormone that has a great role in calcium and phosphorus homeostasis,

bone metabolism and bone development [5], [6]. Recently the role of vitamin D on glucose homeostasis, cardiovascular diseases, immune system and cancer has been reported [7], [8].

In adults, deficiency of vitamin D is associated with higher risks for many cancers, diabetes mellitus (DM), rheumatoid arthritis and multiple sclerosis [9]. In children and infants, Vitamin D insufficiency was reported to be associated with type 1 DM, allergies and atopic diseases (10). Also, children who manifested vitamin D deficiency as rickets were reported to have pneumonia [11].

Indeed, multiple reports suggested the vital role of vitamin D in immune system function and regulation since 1, 25 dihydroxy vitamin D can promote the innate immature response to the pathogen [12]. Besides, multiple studies have

identified an association of respiratory infectious disease and inadequate serum vitamin D in non-rachitic children [13], [14]. Biomarkers, applied in synergy with clinical signs and symptoms of pneumonia may provide extra data on disease severity and the differentiation between bacterial and viral aetiology [15], [16]. Pentraxin 3 is known as an acute-phase mediator that rapidly increases in inflammatory and infectious disorders [17], [18].

However, few studies regarding this link among neonates have been found. Given that this study was designed to evaluate the serum level of 25 hydroxy-vitamin D in neonates with pneumonia and to assess its correlation with serum levels of Pentraxin 3 as a mediator of acute inflammation.

Subjects and Methods

Thirty-three neonates diagnosed to have late-onset pneumonia were recruited from NICU in El Galaa Teaching Hospital. 30 healthy neonates of matched age and sex were enrolled as a control group. Parental written informed consent was obtained from all study participants and the study was approved by the medical ethical committee of the National Research Center, Cairo, Egypt.

The inclusion criteria were as follows: age between day one and one month, clinical signs suggestive of pneumonia such as tachypnea, abnormal breath sounds, and radiological confirmation of pneumonia according to the WHO criteria for the standardised interpretation of pediatric chest radiographs for pneumonia diagnosis. Infants with underlying chronic respiratory disease were excluded from this study.

All participants were subjected to full history taking and full clinical examination. Culture and sensitivity test was done to confirm the aetiology whether bacterial or nonbacterial pneumonia. Venous blood samples (3 cm) were taken from each infant participating in the study and were divided into two aliquots. The first aliquot 1 ml of venous blood was used for determination of CBC. The second aliquot 2ml of venous blood was left to clot, and then the serum was separated by centrifugation and stored at -20°C for detection of serum vitamin D, Pentraxin 3 and CRP levels.

Statistical analysis

Analysis of data was performed by using Statistical Package for the Social Science SPSS version 16.G. Data were presented as a mean and standard deviation. Chi-square test was conducted for detecting the significant difference in the distribution between categorical variables at P-value < 0.05.

Continuous variables were compared by t-test (for normally distributed data). Spearman correlation was used to assess the correlations between non-normally distributed qualitative variables.

Results

The study group comprised 33 neonates with pneumonia aged 24.8 ± 4.6 days. They were 12 (36.4%) males and 21 (63.6%) females. The mean of their gestational age was 37.5 ± 1.8 weeks and 11 of them (33.3%) delivered normally and 22 (66.7%) by caesarian section (CS). The study also included 30 controls matched for age and sex with the patient group as delineated in Table 1. Regarding blood culture of cases, 22 neonates had positive blood cultures for bacteria: *Staphylococcus aureus* (30%), *Klebsiella pneumonia* (25%), *Pseudomonas* (20%), *Acinetobacter* (15%), *E. coli* (10%).

When it comes to laboratory findings of both patient and control group, haemoglobin levels were significantly lower while TLC and CRP levels were higher in cases in comparison to controls. Patients with pneumonia also showed significantly lower levels of vitamin D compared to controls; however, the patient group had significantly higher levels of Pentraxin 3 compared to controls, (Table 1).

Table 1: Demographic and laboratory data of the studied groups

Descriptive data Items	Cases n = 33 (Mean \pm SD) (Range) n (%)	Control n = 30 (Mean \pm SD) (Range) n (%)	Statistical test	P-value
	Gestational age (Wks)	37.5 \pm 1.8		
Age (days)	24.8 \pm 4.6	26.1 \pm 6.1	t = -0.7	0.5
Mode of delivery				
NVD	11 (33.3%)	10 (33.3%)	$\chi^2 = 0$	1.0
CS	22 (66.7%)	20 (66.7%)		
Sex				
Male	12 (36.4%)	14 (46.7%)	$\chi^2 = 0.7$	0.4
Female	21 (63.6%)	16 (53.3%)		
Hemoglobin (g/dl)	9.8 \pm 1.4	13.3 \pm 1.8	t = 4.2	< 0.01*
TLC ($\times 10^9$ /L)	12.2 \pm 3.5	6.9 \pm 1.6	t = 3.3	0.002*
Serum CRP (mg/dl)	29.7 \pm 4.2	4.1 \pm 1.0	t = 5.1	< 0.01*
Serum 25 (OH) D ($\mu\text{g/L}$)	9 \pm 2.1	14.1 \pm 2.8	t = -8	< 0.01*
Serum Pentraxin3 ($\mu\text{g/L}$)	29.1 \pm 4.8	12.6 \pm 3	t = 3.7	< 0.01*

* (P \leq 0.05) is significant.

According to Table 2, mechanically ventilated patients revealed significantly lower vitamin D and higher pentraxin 3 compared to free oxygen patients.

Table 2: Comparison between serum vitamin D and Pentraxin3 in mechanically ventilated patients and patients on free oxygen

Variable	Mechanically ventilated patients N = 14 (Mean \pm SD)	Patients on free oxygen N = 19 (Mean \pm SD)	P-value
Serum 25 (OH) D ($\mu\text{g/L}$)	7.7 \pm 1.8	9.1 \pm 2.1	0.05*
Serum Pentraxin3 ($\mu\text{g/L}$)	32.2 \pm 2.6	26.4 \pm 3.7	0.02*

* (P \leq 0.05) is significant.

Regarding hospital stay, it had significant negative correlation with serum vit D ($r = -0.4$, P value = 0.04) and significant positive correlation with serum pentraxin 3 ($r = 0.6$, P value < 0.01) and as delineated in Figure 1 (top), (middle) respectively. Finally a significant negative correlation between serum Vitamin D and Pentraxin 3 was found ($r = -0.4$, P value = 0.01) (Figure1: bottom).

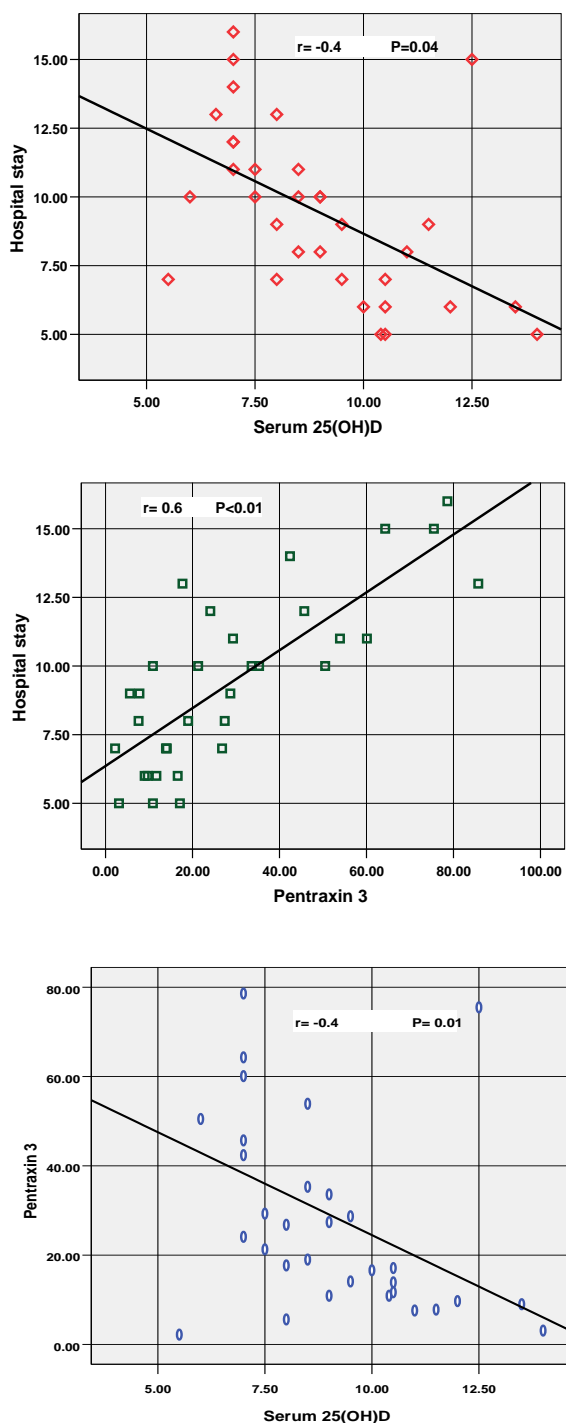


Figure 1: Correlation between serum vitamin D and a hospital stay of neonates with pneumonia (top); Correlation between serum Pentraxin 3 and hospital stay of neonates with pneumonia (middle); Correlation between serum vitamin D and Pentraxin 3 (bottom)

Discussion

The current case-control study aimed to study vitamin D in neonates with pneumonia, and the results showed that serum vitamin D was significantly lower among patients with pneumonia compared to controls and in patients on mechanical ventilation compared to patients on free oxygen. Also, serum vitamin D was negatively correlated with the duration of hospital stay. Similarly, (Lezhenko et al., 2016) reported that children at an early age with low levels of vitamin D are at risk for pneumonia since significant lower concentrations of 25-hydroxyvitamin D were detected in children with community-acquired pneumonia compared with healthy controls [19]. (Dinlen et al., 2016) Also assessed serum 25 (OH) D levels in newborns with pneumonia and their mothers and observed a lower concentration compared to healthy newborns and their mothers [20]. In the same point of view (Mohamed and Al-Shehri, 2013) tested cord blood of 206 newborns for 25 (OH) D and reviewed their medical records during the early 2 years of life and noticed that lower level of 25 (OH) D in cord blood was associated with higher risk for acute lower respiratory tract infection (LRTI) in early life [21]. Indeed, deficiency of vitamin D in pregnant women has been reported to rise respiratory tract infection risk in their offspring as vitamin D can modulate the expression of specific tolerogenic genes during pregnancy that related to diseases other than congenital rickets [22], [23].

The current hypothesis of lower vitamin D is a risk factor for neonatal pneumonia, and its poor prognosis can also be confirmed by the meta-analysis of (Charan et al., 2012) which showed that Vitamin D supplementation could decrease the events related to respiratory tract infections [24]. Besides the systematic review of (Christensen et al., 2017) reported that supplementation of vitamin D during pregnancy could prevent respiratory tract infection of offspring [25]. A more recent systematic review and meta-analysis of (Jat, 2017) showed a significant correlation between vitamin D concentrations and both the incidence and severity of LRTI [26].

In contrast to the current findings, (McNally et al., 2009) did not observe a difference in vitamin D levels between the children with LRTI and controls but vitamin D deficiency was noticed to be significantly associated with admission to the pediatric ICU [27].

Regarding pentraxin 3, it was significantly elevated in patients with pneumonia compared with controls and in mechanically ventilated patients compared to free oxygen ones. Moreover, it was positively correlated with the duration of hospital stay. Similarly, (Tekerek et al., 2018) detected higher levels of Pentraxin 3 among patients with ventilator-associated pneumonia (VAP) compared to controls. [28]. By the same way, (Lin et al., 2013) reported that pentraxin 3 is a biomarker for VAP that correlated with

sepsis severity and was an independent predictor for VAP mortality by multivariate Cox regression analysis [29].

Finally, the present study was able to delineate a significant negative correlation between serum vitamin D and serum Pentraxin 3. Pentraxin 3 is known as an inflammatory biomarker that can be easily used to assess the severity of lung injury [30], [31] and this noticed correlation can confirm the role of vitamin D in neonatal pneumonia.

In conclusion, from the above results, it is now clear that inadequate concentrations of vitamin D in neonates may be associated with higher risks for pneumonia. Also, lowers levels can be a predisposing factor for the need for mechanical ventilation and longer hospital stay. So we can conclude that maternal prenatal/postpartum vitamin D supplementation may be a feasible primary preventive strategy to reduce pulmonary infections in the neonatal period.

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