RESEARCH PAPER

Vitamin D Levels and Cardiopulmonary Status in Infants With Acute Bronchiolitis

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Background: To assess association of vitamin D deficiency with cardiac and pulmonary status in infants with acute bronchiolitis. **Methods**: Infants hospitalized with acute bronchiolitis were enrolled and classified as those with serum 25-hydroxyvitamin D (25-OHD) below or equal and above 20 ng/mL. The primary outcomes were cardiopulmonary involvement defined by elevation of NT-ProBNP, alteration of echocardiographic parameters and respiratory support requirements. The secondary outcomes were the need for PICU admission and duration of hospitalization. **Results**: 92 (50 males) infants with median (IQR) age of 1 (0.5-3) month were included with median (IQR) serum 25-OHD level 27.4 (11.4-40.3) ng/mL. 43 (47%) patients had serum 25-OHD level below 20 ng/mL with left ventricle dysfunction (*P*=0.008), right ventricle dysfunction (*P*=0.008) and pulmonary hypertension (*P*=0.007) on echocardiography more commonly than those with serum 25-OHD ≥20 ng/mL. The median (IQR) serum NT-ProBNP levels were higher in those with low 25-OHD levels than normal 25-OHD levels [2232.2 (461.4-4313.3) and 830.4 (312.7-2579.5)], respectively *(P*=0.003). Low 25-OHD levels were associated with increased risk for PICU admission (OR 3.9 (95% CI 1.5-10.1); *P*=0.004), higher rates of non-invasive ventilation (*P*=0.048) and mechanical ventilation (*P*=0.005) and longer duration of hospitalization (*P*=0.015). **Conclusion:** Low serum vitamin D level was associated with clinical severity and impaired cardiac and pulmonary status in infants with acute bronchiolitis.

Keywords: *Heart failure, NT-Pro BNP, Troponin, Vitamin D deficiency; Ventricular dysfunction.*

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Acute bronchiolitis is a respiratory infection commonly caused by Respiratory syncytial virus (RSV). It is the most frequent cause of hospitalization in infants and treatment is mainly supportive [1].

Recent evidence suggests that vitamin D has immunomodulatory properties that attenuates the intensity of the inflammatory response in acute respiratory tract infections [2,3]. Hypovitaminosis D is associated with heart failure, ventricular dysfunction and pulmonary hypertension in chronic diseases such as diabetes, congenital heart disease and chronic kidney disease [4,5]. Recently, we observed that cardiac dysfunction and pulmonary hypertension could predict adverse outcomes in infants hospitalized with acute bronchiolitis [6,7]. Therefore, we hypothesize that a plausible relationship could exist between vitamin D deficiency and altered cardiovascular status.

The purpose of this study was to explore the association between serum 25-hydroxyvitamin D (25-OHD), pulmonary hypertension status and myocardial dysfunction, and worse clinical outcomes in infants with acute bronchiolitis.

METHODS

This observational study evaluated infants at the pediatric department of a tertiary university-affiliated hospital in Spain, who were admitted with acute bronc-hiolitis between October 1, 2018 and March 31, 2020.

The study was approved by the Institutional Review Board. Informed written parental consent was obtained for all cases before inclusion in the study. Eligible infants were diagnosed and treated as per standard guidelines [1]. Patients previously diagnosed with malnutrition, chronic heart disease, pulmonary, kidney, endocrine and metabolic diseases, a previous episode of acute bron-chiolitis, and with incomplete medical records were excluded.

All patients underwent clinical, laboratory, microbiologic and echocardiography evaluation within the first 24 hours of admission. Biochemical data including serum 25-

hydroxyvitamin D (25-OHD) calcium, phosphorus and N-terminal pro hormone B-type natriuretic peptide (NT-proBNP) levels were recorded. Serum 25-OHD levels of less than 20 ng/mL was defined as hypovitaminosis D.

Bronchiolitis score of Sant Joan de Déu hospital (BROSJOD) was used to assess the respiratory state severity at admission [8]. A BROSJOD score greater than 10 points was indicative of a severe clinical state. Polymerase chain reaction (PCR) analysis of naso-pharyngeal swabs for respiratory viruses was routinely analyzed in all patients. Pediatric intensive care unit (PICU) admission was defined by the need of advanced respiratory support or presence of apneas.

Standard techniques to obtain M-mode, two-dimensional and Doppler (colour, pulsed, continuous and TDI) echocardiograms were performed by a single experienced pediatric cardiologist, who was blinded to the patient's clinical profile. Images were obtained using a Phillips IE33 ultrasound scanner with an 8 or 12-MHz sectorial transducer. All echocardiographic measurements represent the average of three beats.

The primary outcome was the identification of cardiovascular involvement defined by elevated levels of NT-ProBNP and/or detection of myocardial dysfunction or pulmonary hypertension on echocardiography. Secondary outcomes were the need for PICU admission and the duration of hospitalization. Due to the skewed distribution of NT-ProBNP, we carried out a base 10 logarithmic transformation to achieve normal distribution, and this value was used in the statical analysis.

Statistical analysis: Statistical analyses were performed using Stata software (StataCorp. 2014. Stata Statistical Software: Release 14). Continuous data were presented as median (IQR) or mean (SD) after testing for normality with the Shapiro-Wilk test. Categorical data were presented as frequencies and percentage. The comparison of mean was performed using Student t-test or Wilcoxon Mann-Whitney test as appropriate. Proportions were compared using the Chi-square test or exact methods. Pearson or Spearman coefficients were used to assess correlations between continuous data. A *P* value <0.05 was considered statistically significant.

RESULTS

During the study period, 149 infants were assessed for

Table I Baseline Characteristics and Outcome of Infants With Bronchiolitis

Variable	*Serum Vitamin D level*		
	<20 ng/mL (n= 43)	*>20 ng/mL (n=49)*	*P value*
Age,[a] mo	1 (0.5-1)	2 (1-4)	< 0.001
Weight,[a] kg	4.5 (3.6-5.3)	5.5 (4-6.2)	0.006
Comorbidity	9 (21)	10 (21)	0.95
BROSJOD score[a]	8 (5-11)	7 (5-9)	0.18
Respiratory syncytial virus positive	33 (77)	37 (75)	0.97
Bacterial superinfection	3 (7)	4 (8)	0.8
Apneas	5 (12)	0	0.01
SpO2[a]	97 (88-99)	95 (90-99)	0.83
pH	7.30 (0.06)	7.34 (0.05)	0.003
pCO2[a]	58 (48-63)	46 (41-54)	0.002
Nebulization[a]	20 (46)	33 (67)	0.1
Antibiotics	3 (7)	4 (8)	0.81
Oxygen (nasal canula)	16 (37)	33 (67)	0.004
High flow nasal canulae	1 (2)	2 (4)	0.653
Pediatric intensive care unit admission	20 (47)	9 (18)	0.003
Pediatric intensive care unit stay,[a] d	6 (4-12)	5.5 (3.5-8)	0.44
Non-invasive ventilation	14 (33)	8 (16)	0.048
Mechanical ventilation	6 (14)	0 (0)	0.005
Duration of hospitalization,[a] d	7 (2-11)	4 (2-6)	0.01

**Data presented n (%) or [a]median (IQR). BROSJOD (Bronchiolitis score of Sant Joan of Deu hospital); LU (Lung ultrasound).*

eligibility of whom 57 were excluded as we had insufficient blood sample, resulting in a study sample of 92 (50 boys, 19 with prematurity). The median (IQR) age was 1 (0.5-3) months. The most prevalent (70%) causative agent was RSV. Twenty nine (32%) patients required PICU admission for a median (IQR) duration of 6 (4-9) days. Twenty two (25%) infants required non-invasive ventilation (NIV), and 6 (6.5%) required mechanical ventilation (MV). **Table I** compares the baseline characteristics as per serum 25-OHD levels.

The median (IQR) 25-OHD levels were 27.4 (11.4-40.3) ng/mL, with hypovitaminosis D seen in 43 (47%) infants. Hypovitaminosis D was associated with increased risk for PICU admission [OR 3.9, 95% CI 1.5-10.1; *P*=0.004]. The echocardiographic measurements and cardiac biomarkers are compared as per vitamin D status in **Table II**. A significant negative correlation was seen between log-NT-pro BNP and 25-OHD levels (r=-0.35, *P*=0.002).

DISCUSSION

In this study, hypovitaminosis D was associated with impairment of myocardial function, increased pulmonary pressures, higher risk of PICU admission for advanced respiratory support, and prolonged hospitalization.

Severe lung involvement can be accompanied by a significant impairment of the cardiovascular status in acute bronchiolitis [9]. Increased troponin I levels and echocardiographic measures indicative of pulmonary hypertension and right ventricular diastolic dysfunction have been observed earlier in patients with hypoxia and acidosis [10]. The wide-ranging functions of microRNAs in the cardiovascular system have provided new perspectives on disease diagnostics for a variety of cardiovascular disorders [10].

Cardiac biomarker NT-proBNP is secreted by myocytes in response to increased stress, and it is an accurate diagnostic and prognostic biomarker of heart failure and pulmonary hypertension [11,12]. Notably, we observed that infants with hypovitaminosis D had increased rates of abnormal echocardiographic parameters indicative of pulmonary hypertension and myocardial dysfunction, with increased values of NT-proBNP. Vitamin D exerts its action through the vitamin D receptor, which has also been localized in the cardiovascular system on vascular smooth muscle cells, endothelial cells, and cardiomyocytes. Vitamin D exerts cardioprotective actions and regulates cardiac function by modulating serum and calcium parathyroid hormone levels. Vitamin D also exerts an inhibitory action on the renin-angiotensin-aldosterone axis in vitro, such that hypovitaminosis D can increase the renin levels promoting arterial hypertension, myocardial hypertrophy and raised plasmatic levels of natriuretic peptides [13,14]. Vitamin D deficiency is associated with the development of dilated cardiomyopathy with severe hypocalcemia in infants with nutritional rickets and in the development of pulmonary hypertension [14,15].

It is possible that hypovitaminosis favors a baseline subclinical myocardial dysfunction in infants that could worsen in the acute respiratory setting leading to the development of a severe course of the disease. Nevertheless, the pathophysiology of hypovitaminosis D causing altered cardiovascular status might be different in acute respiratory disease and in chronic cardiovascular setting. The lack of immunomodulatory effect of vitamin D in deficiency states would lead to more severe airway inflammation and subsequent, hypoxemia, and acidosis, leading to raised pulmonary pressures and myocardial dysfunction [14].

Table II Echocardiographic Parameters and Cardiac Biomarkers in Infants With Bronchiolitis

Variable	*Serum vitamin D level*		*P value*
	<20 ng/mL (n= 43)	*>20 ng/mL (n=49)*	
Left ventricle			
FS, %	43 (39-57)	41 (38-55)	0.702
S‘, cm/s	8.5 (7-11)	10 (8-12)	0.030
E´, cm/s	8 (7-10)	10 (9-11)	0.020
A´, cm/s	9 (7-11)	9 (8-11)	0.607
MPI, %	0.48 (0.40-0.63)	0.41 (0.36-0.56)	0.008
Right ventricle			
TAPSE	14 (12-16)	15 (12-16)	0.293
S‘, cm/s	10 (7-11)	11 (8-12)	0.039
E´, cm/s	10 (8-11)	10 (8-11)	0.823
A´, cm/s	9 (7-10)	9 (8-11)	0.100
MPI, %	0.49 (0.41-0.68)	0.40 (0.35-0.58)	0.008
Pulmonary hypertension			
TRJG, mmHg	21 (19-37)	24 (18-37)	0.725
ATET	0.32 (0.08)	0.36 (0.07)	0.007
LVEI	1.2 (1.06-1.41)	1.03 (1-1.27)	0.007
RVLVr	0.58 (0.48-0.68)	0.48 (0.40-0-6)	0.003
Cardiac biomarkers			
NT-proBNP, pg/*mL*[a]	2232.2 (461.4-4313.3)	830.4 (312.7-2579.5)	0.003
Troponin I, ng/L[b]	19.2 (10.1-41.3)	10.3 (10.1-17.6)	0.163

Data presented in median (IQR). FS (Fraction shortening); S' (Systolic wave); E´(Early diastolic wave); A´ (Active atrial contraction wave); MPI (Myocardial performance index); TAPSE (tricuspid annular plane systolic excursion); TRJG: (Tricuspid regurgitation jet gradient); ATET (Acceleration time/ejection time ratio); LVEI (Left ventricular ejection index); RV/LV (Right/left ventricular end-diastolic diameter ratio); [a]n=92 for NT-proBNP (N-terminal pro-brain natriuretic peptide). [b]n= 92 for troponin.

WHAT THIS STUDY ADDS?

- We found a high incidence of vitamin D deficiency among infants hospitalized with acute bronchiolitis.
- An association was found between low levels of vitamin D and clinical severity.

The present study had few limitations. Few of the included patients were only 15-days-old, and it is likely that their pulmonary pressures were still physiologically raised. As these patients with hypovitaminosis D were younger, age could act as a cofounding factor limiting our results. Besides, up to 20% of the included patients were born prematurely, who could have high pulmonary pressures and subclinical myocardial dysfunction due to a delayed drop of pulmonary vascular resistances and delayed myocardial function maturation. Parathyroid hormone levels were not measured in this study, and therefore, we could not assess the calcium and phosphate metabolism. The details of feeding history, sunlight exposure and dose of vitamin D supplementation were not recorded in the study. There were significant differences in the baseline variables among the study groups, but no statistical adjustments were made for the same.

In conclusion, a high incidence of hypovitaminosis D was observed among infants hospitalized with acute bronchiolitis and a significant association with worse clinical, respiratory, and cardiovascular status was recorded. Further studies are needed to better understand the exact mechanisms and significance of these relationships.

Ethics clearance: IRB, Puerta del Mar Univesity Hospital; No. 82.18, dated Oct 26, 2018.
Contributors: EM, CM, RG: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; EP,RC,RG,FG: collected data and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
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