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Plasma vitamin A levels in deprived children with pneumonia during the acute phase and after recovery

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Abstract

Objective: The aim of this study was to examine the plasma retinol of children in the acute phase of pneumonia and after recovery and to investigate the association between plasma levels of retinol after recovery with socioeconomic variables, nutritional status and severity of pneumonia.

Methods: A prospective cohort study which included 40 low-income hospitalized children with pneumonia, aged 6 months to 5 years. We evaluated: plasma retinol level during the acute phase and after recovery, years of schooling of the head of the family, per capita income, birth weight, nutritional status, hemoglobin levels and severity of pneumonia.

Results: Mean plasma retinol levels were significantly higher after recovery than during the acute phase of infection (1.4±0.6 vs. 1.7±0.6 µmol/l, p = 0.03). The frequency of inadequate plasma retinol levels (< 1.05 µmol/l) was 32.5 and 17.5% for the acute phase and after recovery, respectively. There were no statistically significant associations between plasma retinol deficiency and the clinical and epidemiological variables studied. More severe pneumonia was observed in 30/40 (75%) of the patients. There was no statistically significant association between plasma retinol inadequacy after recovery and severity of pneumonia (4/30 – 13.3% vs. 3/10 – 30.0%, p = 0.34).

Conclusion: Serum retinol levels were significantly higher after recovery than during the acute phase of pneumonia. There was no statistically significant association between the deficiency of serum retinol and the clinical and epidemiological variables studied.

J Pediatr (Rio J). 2005;81(2):162-8: Vitamin A, nutritional status, children, pneumonia.

Introduction

Vitamin A deficiency (VAD) interferes with immunity and with the respiratory epithelium. VAD may lead to squamous metaplasia with subsequent loss of defense mechanisms against microbial invasion and to the development of obstructive phenomena caused by bronchial hyperresponsiveness.[1]

It is commonly known that micronutrient deficiency is associated with the etiology and aggravation of infectious diseases, and that infection is one of the causes of nutrient depletion. Epidemiologically, the most widely investigated deficiencies are those of vitamin A and iron.[2] It has been estimated that 127 million preschool children around the globe suffer from VAD and that 4.4 million have xerophthalmia.[3]

In Brazil, no nationwide survey has been conducted to assess the prevalence of VAD. We know that the northeast and the Vale do Jequitinhonha region have a high VAD prevalence, and that they were included in a national campaign against vitamin A deficiency.[4] Studies with preschool children in the southeastern region (São Paulo and Rio de Janeiro) also show high VAD prevalence rates, which range from 34.6 to 59.1%.[5]

Several randomized controlled studies have shown the positive effects of interventions using large-dose supplement

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of Vitamin A on measles mortality, with a 50% reduction, and on its complications, such as lung diseases, in developing countries.[6] With regard to pneumonias unrelated to measles, a recent meta-analysis has revealed that there is no evidence of the effects of high-dose vitamin A supplementation on the treatment of infants and children aged between 1 month and 6 years in developing countries.[6] In these countries, five million children younger than five years die every year due to respiratory infections, and approximately 70% of these deaths result from pneumonias.[7] In our setting, respiratory infections are extremely prevalent, accounting for 8.6 and 20.2% of the total number of deaths among infants and children aged between 1 and 4 years, respectively.[8]

Acute respiratory infection can be characterized by low serum levels of vitamin A due to several mechanisms, such as: increased consumption for the recovery of the tracheobronchial epithelium damaged by the infectious process;[1] decrease in intake and uptake; deviation of protein synthesis, with predominant production of acute-phase proteins over the reduction in the pool of circulating visceral proteins (e.g.: retinol binding protein - RBP); high consumption of antioxidants, due to the exacerbation of oxidative stress caused by inflammation and infection; and increase in urinary excretion during the acute phase of infection.[9,10]

In the literature, there is some controversy over the clinical effects of low serum concentrations of vitamin A, observed in the acute phase of the infectious process. Studies show that the transient reduction, associated with the acute phase of the infectious process, in serum retinol levels, can combine with retinol stores in the eye and lead to night blindness and retinal dystrophy.[11] Serum levels after the resolution of infections of different severity, or the association of functional tests for the assessment of visual and immunological mechanisms may help elucidate the consequences of vitamin A depletion during the acute phase of infection. Only few studies have investigated this issue in acute respiratory infections.[10]

Thus, the aim of this study was to compare serum retinol levels in the acute phase and after resolution of acute lung infection (pneumonia). It is important to check the association between serum retinol levels after the resolution of the infectious process using socioeconomic variables, nutritional status and severity of pneumonia.

Patients and methods

Population and study design

This was a prospective study including 40 infants and children with acute lung infection (pneumonia), aged between 6 months and 5 years, who had been admitted as inpatients to the pediatric ward of a public hospital of Santo André, affiliated with the School of Medicine of ABC Paulista, state of São Paulo, treated between May and August 2003. The same group of patients was assessed in two different time periods: during the acute phase of the disease and at least 15 days after hospital discharge (resolution of the infectious process), considering serum retinol levels. Moreover, clinical and epidemiological information was analyzed and compared to serum retinol levels.

The mean levels of serum retinol, during and after the acute phase of lung infection, were compared using Student's *t* test, for which a p value less than 0.05 was considered significant, with a 7% difference between mean retinol levels in the two periods analyzed.[12] Based on this level of significance and on a 90% power, the sample size consisted of 23 cases.[13]

Of the 60 infants and children admitted as inpatients to the pediatric ward and who met the inclusion criteria, 20 did not participate in the study because their parents did not agree to their inclusion. The analyzed sample corresponded to 66% of the total number of eligible infants and children, which renders the study population representative.[14] The infants and children who did not participate in the study were compared as to their age, sex, and severity of the disease. No statistically significant differences were observed, thus reducing the possibility of a selection bias.[15]

After clinical assessment, parents or surrogates received information about the study objectives and protocol and were asked to sign an informed consent for the participation of their children in the study.

The clinical diagnosis of pneumonia was established based on clinical and radiological criteria proposed by the World Health Organization (WHO).[14]

Infants and children with chronic diseases, such as kidney, liver, heart, lung, and blood diseases, and acquired immunodeficiency syndrome, were not included in the study. Neither were those who received vitamin A in drug form before and between hospital admission and reassessment, and those who needed transfusion of blood or blood products.

The study protocol was approved by the ethics committees of Universidade Federal de São Paulo and Faculdade de Medicina do ABC.

Personal data

A precoded questionnaire was applied to parents and surrogates during hospital stay and during reassessment (after hospital discharge). The questions concerned socioeconomic factors, gestational and neonatal history and data about hospital admission.

Clinical data related to outcome were obtained from medical records. With regard to anthropometric data, weight and height information was collected prospectively following the WHO recommendations.[16] Based on these data, z scores for weight and height (ZWH), and height for age (ZHA) were calculated, using the Center for Disease Control and Prevention (CDC, 2000),[17] and the cutoff points for the assessment of nutritional status proposed by the WHO (1995),[16] as a reference.

Control variables

The various independent variables were related to the analyzed outcome (serum retinol after hospital discharge).

The following variables were analyzed:

1) Socioeconomic variables: monthly per capita income in Reais, level of education of the household head in complete years, type of house (wooden and others), health conditions in the household and use of day care services. Housing conditions were appropriate if the household had treated water, sanitary sewer system, and an indoor bathroom.
2) Gestational and neonatal variables: gestational age, birthweight, and breastfeeding.
3) Hemoglobin levels at reassessment.
4) Severity of pneumonia: the risk of death from pneumonia described in other epidemiological studies was considered a sign of increased severity.[18,19]

Thus, patients were subdivided into groups of more and less severity, based on the presence of two or more of the following situations:

- Necessity to change antibiotics;
- Age between 6 and 12 months;
- Presence of pulmonary complications, such as pleural effusion, atelectasis, pneumothorax, pneumatocele, abscess.

All radiological exams were assessed by the same author (pediatrician).

Biochemical quantification of retinol and complete blood count

For the quantification of serum retinol, 5 ml of blood was collected after an eight-hour fasting period, by way of venipuncture, in a dim-light environment. Light-protected tubes containing heparin sodium were used.[20] High-performance liquid chromatography (HPLC) was used for the determination of serum vitamin A levels.[21] A cutoff point of 1.05 µmol/l (30 µg/dl) was used for definition of low (inappropriate) serum vitamin A levels. [22] For the complete blood count, 2 ml of blood was collected in a tube containing EDTA, whereas the quantification of hemoglobin levels was made using the cyanmethemoglobin method.[23]

Statistical analysis

Epi-Info (version 3)[24] and STATA 8.0[25] were used for the statistical analysis. To compare retinol, in the categorized form, with the clinical and epidemiological variables, we used the chi-square test and Fisher's exact test. To compare retinol levels in the acute phase and after resolution of pneumonia, we used the paired *t* test. In all tests, the significance level was set at 0.05 or 5%.

Results

In the study population, we observed that the median age was 22 months, with a mean of 25 months; 50% (20/40) of the children were male, 12.5% (6/40) had low birthweight (LBW) and 45.9% (19/37) had a total breastfeeding time lower than 6 months (Table 1). With regard to socioeconomic background, the mean per capita income in reais was R$ 147.00 (approximately 0.5 minimum wage) and 60% (24/40) of household heads had less than 8 years of schooling. Adequate health conditions were found in only 52.2% (21/40) of the households (Table 1).

As to the nutritional status, 7.5 and 20% of the analyzed children had moderate to severe malnutrition and short stature, respectively. The mean length of hospital stay was 10.9 days and the mean time for reassessment was 62 days (Table 1).

No statistically significant association was observed between serum retinol deficiency, after resolution of the infectious process, and the clinical and epidemiological variables (Table 2).

Of 27 children who showed appropriate serum retinol levels in the acute phase,15% had inadequate levels. Among 13 children with inadequate serum retinol levels in the acute phase, 77% showed adequate levels after recovery (Table 3).

The mean serum retinol level after resolution of the infectious process was significantly higher compared to the acute phase of infection (1.7±0.6 *versus* 1.4±0.6 µmol/l, p = 0.03) (Figure 1). The frequency of inadequate serum retinol levels (below 1.05 µmol/l) amounted to 32.5 and 17.5% in the acute phase and after resolution of the infectious process, respectively (Table 1).

Severe pneumonia was observed in 75% (30/40) of the assessed children (Table 2). No statistically significant difference was found between inadequate serum retinol levels, after the resolution of the infectious process, and severity of pneumonia (4/30 – 13.3% *versus* 3/10 – 30.0%, p = 0.34).

Discussion

Vitamin A is stored in the liver and carried to peripheral tissues by the retinol-binding protein. When hepatic reserves of vitamin A decrease critically, serum retinol also decreases and, therefore, it can be used as a sign of hepatic deposition.[26]

The WHO recommends values lower than 0.7 µmol/l as a cutoff point for the identification of retinol deficiency. However, at levels below 1.05 µmol/l, there is a marginal involvement of hepatic reserves; thus, at this moment, no classic VAD manifestations are observed. Nevertheless, there are immune system and tissue repair disorders, which affect mainly the respiratory epithelium.[1,27]

The study shows that the mean serum retinol level in the period of resolution of pneumonia was significantly higher in the acute phase of infection. We also observed low serum retinol levels in 32.5 and 17.5% of the children during the acute phase and after resolution of pneumonia, respectively.

One of the limitations of this study was the absence of a control group. Therefore, the model proposed herein does not allow determining whether the low serum levels observed after resolution of the infectious process in

Table 1 - Population features (n total = 40)

Variable	n	%	Mean	(SD)
Age (months)	40		25	(15)
Per capita income (R$)	40		147.6	(136.2)
Birth weight (< 2,500 g)	5	12.5	3146	(849)
Sex (male)	20	50.0		
Did not go to nursery school	31	77.5		
Household head schooling (< 8 years)	24	60.0		
Household (wooden house)	12	30.0		
Health condition (inadequate)	19	47.5		
Gestational age (prematurity)	5	12.5		
Total breastfeeding (< 6 months)	19 *	45.9		
Nutritional status	40			
ZWH (< -2)	3	7.5	-0.3	(1.1)
ZH (< -2)	8	20.0	-0.7	(1.6)
Antibiotic Change	14	35.0		
Pulmonary complications	17	42.5		
Time of hospital stay (days)	40	10.5	(5.9)	
Interval between hospital stay and reassessment (days)	40	62.5	(35)	

SD = standard deviation; ZWH = z scores for weight and height; ZH = z score for height.
* Breastfeeding - n = 37

Table 2 - Association between serum retinol (µmol/L) and clinic-epidemiologic variables after resolution of the infectious process

Variable	n	Retinol (< 1.05)		Retinol (≥ 1.05)		p
		(n = 7)		(n = 33)		
Age (months)	40	20,7	(11.8)	25.8	(15.2)	0.41
Per capita income (R$)	40	131,7	(22.5)	150.9	(25.8)	0.74
Sex						
Female	20	5	(25%)	15	(75%)	0,41
Male	20	2	(10%)	18	(90%)	
Schooling (head of the family)						
< 8 years	24	4	(16.7%)	20	(83.3%)	0.59
≥ 8 years	16	3	(18.7%)	13	(81.3%)	
Weight at term						
< 2,500 g	10	3	(30%)	7	(70%)	0,34
≥ 2,500 g	30	4	(13.3%)	26	(86.7%)	
Gestational age						
< 37 weeks	5	1	(20%)	4	(80%)	0.63
≥ 37 weeks	35	6	(17.2%)	29	(82.8%)	
Z score H/A						
< -2 z	8	1	(12.5%)	7	(87.5%)	0.67
≥ -2 z	32	6	(18.7%)	26	(81.3%)	
Pneumonia severity						
More severe	30	4	(13.3%)	26	(86.7%)	0.34
Less severe	10	3	(30.0%)	7	(70.0%)	
Hb at reassessment						
<11 g/dl	19	4	(21%)	15	(79%)	0.65
≥ 11 g/dl	21	3	(14.3%)	18	(85.7%)	

H/A = z score for height/age.

17.3% of the children resulted from the depletion caused by the infectious process or whether they already existed and then predisposed to lung infection.[28]

According to the literature, preschool children are at greater risk for VAD than infants.[29] In our study, the high frequency of low serum retinol levels at early ages is an interesting finding, since the median age of patients was 25 months.

The validity of the comparisons made in this study relies on the homogeneity of the sample, especially regarding unfavorable socioeconomic conditions. The mean per capita income corresponded to 0.5 minimum wage, which is below the poverty line.[30]

The level of education of the household head was less than eight years in 60% of the sampled individuals, with no statistically significant association with low retinol levels after resolution of infection. Cohen et al. demonstrated that, in isolation, good maternal levels of income and of education were significantly associated with lower risk of xerophthalmia in Bangladeshi children. However, studies carried out in the northeastern region of the country did not find any association of VAD with level of education and per capita income.[31] The lack of such correlation in Brazilian pediatric populations can be explained by the greater homogeneity of the analyzed samples with regard to income and level of education.

In the literature, LBW is regarded as an important risk factor for the development of respiratory infections and for the compromise of hepatic reserves of some micronutrients, such as vitamin A;[7] however, in our study, we did not observe any association between the severity of LBW and vitamin A.

Impaired height growth (ZH < -2) was observed in 20% of the assessed children, without any association with inappropriate serum retinol levels. It is widely known that the association of VAD and ZH < -2 increases the risk of infant mortality. Other studies did not find an association between compromised nutritional status and VAD.[32]

Vitamin A is involved in the pathogenesis of anemia through different mechanisms: stimulus to the growth and differentiation of erythrocyte progenitor cells, maximization of the immune response, reduction of anemia associated with infection and mobilization of hepatic iron reserves.[33] The interaction between iron and vitamin A may be one of the factors implicated in the high prevalence of anemia observed among the analyzed children (51.3%), after resolution of the infectious process, although no association was found in our study between inadequate retinol levels and hemoglobin level.

Table 3 - Development of cases according to the adequate serum retinol levels after recovery (cutoff in 1.05 µmol/l)

Acute phase	Recovery phase		
	≥ 1.05 µmol/l	< 1.05 µmol/l	Total
≥ 1.05 µmol/l	23	4	27
< 1.05 µmol/l	10	3	13
Total	33	7	40

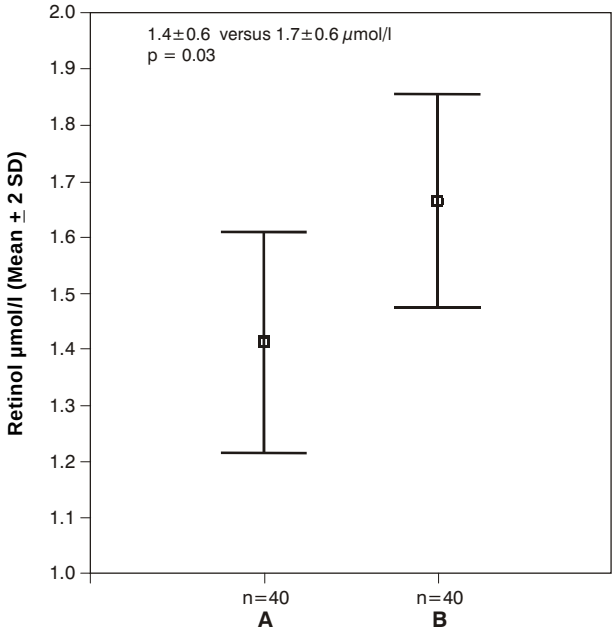

Figure 1 - Mean serum retinol level after resolution of the infectious process (B) in infants with acute phase pneumonia (A)

Vitamin A also plays an important role in immunological function, is essential to cell membrane stability, and influences growth and repair of epithelial cells. Specifically, in the respiratory epithelium, VAD reduces the proliferation of basal cells and mucus-producing cells, resulting in squamous metaplasia. Impaired integrity of the respiratory tract mucosa increases vulnerability to infectious and obstructive complications, elevating morbidity and mortality rates.[28]

In the present study, no correlation was found between the severity of pneumonia and adequacy of retinol levels after resolution of the infectious process. However, the WHO underscores the participation of severe infectious diseases as cause of acute deterioration of the nutritional status relative to vitamin A.[34]

Even though some evidence shows histopathological damage associated with VAD that are is pronounced in the respiratory tract than in the digestive one, a recent meta-analysis did not demonstrate the impact of megadoses of vitamin A on the incidence of diarrhea, but a slight increase in the incidence of respiratory infections, instead.[35]

Experimental animal studies revealed that in situations of deficiency or chronic excess of vitamin A, cellular and humoral immunity are compromised, predisposing to infectious processes. Furthermore, vitamin A supplementation was associated with the absence of effects and even with the presence of adverse effects on the severity of the disease when used as adjuvant therapy for acute respiratory infections,[36] except for morbidities associated with measles.[37]

In this regard, this study assumes great importance because it improves the knowledge about the behavior of vitamin A in the infectious process, since there is some evidence that contraindicates the nonjudicious use of vitamin A as prophylaxis or adjuvant therapy for acute respiratory infections.

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