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Original

Nutritional status of iron in children from 6 to 59 months of age and its relation to vitamin A deficiency

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Abstract

Objective: **To evaluate the iron nutritional status of children from 6 to 59 months of age and its relation to vitamin A deficiency.**

Method: **Cross-sectional study involving 100 children, living in nine cities in the state of Paraíba, which were selected for convenience to form two study groups: children with vitamin A deficiency (serum retinol < 0.70 µmol/L; n = 50) and children without vitamin A deficiency (serum retinol ≥ 0.70 µmol/L; n = 50). The iron nutritional status was evaluated by biochemical, hematological and hematimetric indices. The cases of subclinical infection (C-Reactive Protein ≥ 6 mg/L) were excluded.**

Results: **Children with vitamin A deficiency had serum iron values statistically lower than the corresponding values in children without deficiency. The other iron nutritional status indices showed no statistical difference according to presence/absence of vitamin A deficiency.**

Conclusion: **The interaction between iron and vitamin A deficiencies was evidenced in the case of circulating iron deficiency (serum iron), suggesting failure in the transport mechanisms of the mineral in children with vitamin A deficiency.**

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Key words: *Iron Deficiency. Vitamin A Deficiency.*

ESTADO NUTRICIONAL DE HIERRO EN NIÑOS DE 6 A 59 MESES DE EDAD Y SU RELACIÓN CON LA DEFICIENCIA DE VITAMINA A

Resumen

Objetivos: **Evaluar el estado nutricional de hierro en niños de 6 a 59 meses de edad y su relación con la deficiencia de vitamina A.**

Métodos: **Estudio transversal, envolviendo 100 niños, residentes en nueve ciudades del estado de Paraíba, seleccionados por conveniencia para conformar dos grupos de estudio: niños con deficiencia de vitamina A (retinol sérico < 0,70 µmol/L; n = 50) y niños sin deficiencia de vitamina A (retinol sérico ≥ 0,70 µmol/L; n = 50). El estado nutricional de hierro fue evaluado a través de índices bioquímicos, hematológicos y hematimétricos. Los casos de infección subclínica (proteína C-reactiva ≥ 6 mg/L) fueron excluidos.**

Resultados: **Los niños con deficiencia de vitamina A presentaron valores medios de hierro sérico estadísticamente inferiores a los valores correspondientes en niños sin deficiencia. Los otros índices del estado nutricional de hierro no mostraron diferencia estadística según la presencia/ausencia de deficiencia de vitamina A.**

Conclusión: **La interacción entre las carencias de hierro y de vitamina A estuvo evidenciada en los casos de deficiencia de hierro circulante (hierro sérico), sugiriendo insuficiencia en los mecanismos de transporte del mineral en niños con deficiencia de vitamina A.**

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Palabras clave: *Deficiencia de hierro. Deficiencia de Vitamina A.*

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Abbreviations

CI: Confidence Interval.
LSD: Least Square Deviance.
MCH: Mean Corpuscular Hemoglobin.
MCHC: Mean Corpuscular Hemoglobin Concentration.
MCV: Mean Corpuscular Volume.
OR: Odds Ratio.
RBP: Retinol Binding Protein.
RDW: Red Cell Distribution Width.
SD: Standard Deviation.
VAD: Vitamin A deficiency.

Introduction

Iron deficiency is the most prevalent nutritional disorder worldwide and the principal cause of anemia in childhood.[1] In spite of affecting a large number of children and women in non-industrialized countries, it is the only nutrient deficiency significantly prevalent in virtually all industrialized nation.[2]

In Brazil, according to data from the National Research of Women and Children Demography and Health,[3] 20.9% of Brazilian preschool children are affected by anemia, being the child population in the Northeast of Brazil more vulnerable to this nutritional deficiency, with prevalence of 25.5%.

The iron deficiency, even without the presence of anemia, causes numerous health problems for children such as fatigue and weakness, due to the bad energy use by muscles, behavioral and cognitive disorders, and deficit in the physical growth.[4]

Several factors might be included in the genesis of this nutritional deficiency to cite: the low iron stores at birth, the fast rhythm of the children growth, the iron interaction with other diet components, the infectious diseases, the obtaining of insufficient iron by means of feed, and even the deficiency of other micronutrients such as vitamin A.[1,5,6]

The vitamin A deficiency (VAD) is a public health problem in many developing countries, affecting mainly children under five years old.[7] Brazil is considered as a risk area of sub clinic VDA.[8] It is estimated that 17.4% of the Brazilian children population has shown inadequate levels of vitamin A, with the highest prevalence of VAD observed in the Southeast (21.6%) and Northeast regions (19.0%).[3]

The main causes of VAD can be summarized into two broad categories of aspect: inadequate diet and the presence of infectious processes. The inadequate diet includes poor food intake of vitamin A food sources as well as inadequate intake of foods containing important nutrients for its bio use. In children, beyond the need of a food that accompanies the period of growth and development, the infectious processes which are common in this stage of life constitutes a complicating factor, damaging the vitamin A use by the organism.[9,10]

VAD, even in its subclinical form, can lead to increased morbidity and mortality from infectious diseases and diarrhea. In extreme cases, this nutritional deficiency can direct to blindness due to irreversible loss of cornea[11]. Moreover, by mechanisms not yet completely understood, this deficiency can induce to an iron deficiency anemia.[6,12]

It is postulated that the association between VAD and iron deficiency anemia is due to the fact that vitamin A benefits erythropoiesis, interferes in the modulation of iron metabolism and improves the immune response against infectious disease.[6,12,13]

Vitamin A increases the depletion of liver iron storage, making this mineral available for the hemoglobin synthesis, events that directly benefit the iron metabolism and the erythropoiesis. This way, in individuals with VAD, it is possible that a functional iron deficiency is developed even when the mineral storage are present at normal levels.[6,12]

Since the vitamin A is an important immuno modulator nutrient, in the VDA occurrence, the infection can be more easily installed. Consequently, the individual would become more vulnerable to the development of anemia of infection which is characterized by low concentrations of transferrin and ferritin increase levels. This process generates an accumulation of iron in the liver, this mineral rendered unavailable for erythropoiesis, which contributes to the development of anemia. In addition, the infectious processes can interfere with the synthesis of Retinol Binding Protein (RBP), and, in consequence, triggers the occurrence of VDA, a risk factor for anemia of infection.[12]

In this context, this study aims to evaluate the iron nutritional status of children from 6 to 59 months of age and its relation to vitamin A deficiency.

Methodology

This is a cross-sectional study, forming part of a wider research project, population-based research, developed in the state of Paraíba, in the period from January to April 2007, in order to assess the implementation of the "More Vitamin A-National Vitamin Supplementation Program", as well as determine the prevalence of vitamin A deficiency, anemia and malnutrition in children in the state.

Participants and sample

The sample of the original project consisted of 1,324 children, aged 6 to 59 months of age, who live in the cities of three regions of Paraíba. The children were randomly selected according to sampling type of multiple steps types. For this selection, it was estimated the population data of these cities in the state, provided by the Brazilian Institute of Geography and Statistics, for the year 2006. Subsequently, it was carried out a

survey of the number of children 6-59 months of age (15% of the population), living in the urban area, with their accumulated populations. After calculating the sampling interval, the randomization of the cities was conducted, then the census tracts, households and children. The drawn cities were: Conceição, Belém do Brejo do Cruz, Boa Ventura, Pedra Branca, São José de Espinharas, Malta, Patos, João Pessoa and Campina Grande.

To compose the sample of the present study, it was initially selected children who had serum retinol levels and hemogram, excluding cases of subclinical infection (C-Reactive protein ≥ 6 mg/dL determined by latex agglutination), with a total of a sample of 991 children. Then, it was selected from these 991 children, and for convenience, a sub-sample of 100 children (50 males and 50 females), 50 children with VAD (retinol < 0.70 µmol/L), and 50 children without VAD (retinol ≥ 0.70 µmol/L).

Instrument of demographic and socioeconomic data collection

The demographic and socioeconomic data come from questionnaires filled in the original study, with parents or guardians.

Evaluation of the nutritional state of iron and vitamin A

The evaluation of the nutritional status of iron and vitamin A was made from biochemical, hematology and hematimetric markers. The biochemical indicators considered were the serum concentrations of retinol, iron and ferritin. The hematological indicators considered were hemoglobin, erythrocytes and hematocrit. The hematimetric indicators considered were Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) and Red Cell Distribution Width (RDW).

It was collected 3 mL of blood by venipuncture, using disposable needles and syringes. Part of the blood sample (2 mL) was collected in tubes without anticoagulant, wrapped in aluminum foil, is used to determine serum concentrations of retinol, iron and ferritin, the techniques of High Performance Liquid Chromatography, turbidimetry and ELISA, respectively. The remaining blood sample (1 mL) was collected in tubes with K_3EDTA anticoagulant and is used to obtain the hematological and hematimetric indicators from hemogram performed from an automatic counter (Sysmex SF-3000, Roche Diagnostics).

It was considered adequate the following reference values: serum retinol ≥ 0.70 µmol/L,[14] serum iron ≥ 50.0 µg/dL, serum ferritin ≥ 14.0 µg/L,[15] hemoglobin ≥ 11.0 g/dL,[16] erythrocytes 4.60-4.80 million/mm^3, hematocrit 34.0-42.0%,[17] MCV 82.0-92.0 fL, MCH 27.0-32.0 pg, MCHC 30.0-35.0 g/dL e RDW 11.0-15.0%.[15]

The analyses of serum retinol and serum ferritin were performed in the Lauro Wanderley University Hospital, Federal University of Paraíba, and the levels of C - Reactive Protein and hemogram were done at the Laboratory of Clinical Analyses, State University of Paraíba.

Data analysis

The obtained information was used for feeding the database using the statistical program Epi Info 6.04b. Data were entered in duplicate, with subsequently evaluation of the consistency of the application using validate (Epi Info 6.04b). Data were then analyzed using the SPSS statistics program version 8.0.

The variables for the population characterization were presented using descriptive statistics (simple frequencies). It was presented markers of nutritional status of iron and vitamin A according to sex and age, using measures of central tendency and dispersion (mean and standard deviation-SD). To check the assumption of normality of the variables involved in the study, it was applied the Kolmogorov-Smirnov test, when necessary. For comparisons between groups, it was applied Student's t-test for comparison by sex and ANOVA for comparison by age. To test the homogeneity of variances, it was applied the Levene test and Least Square Deviance (LSD) was used for post-hoc tests.

For the analysis of indicators according to VAD, it was used Odds Ratio (OR) as a measure of association with their respective confidence interval (CI). The OR's were calculated using logistic regression models. In the first part of the analysis, all OR's were adjusted for sex and age group. Subsequently, it was performed a multivariate analysis, which were inserted in the model all variables with p-value of up to 0.25 in the bivariate analysis. The final model was obtained by the Backward method and all findings were performed considering the significance level of 5%.

Ethical considerations

The project was evaluated and approved by the Ethics Committee in Research of the State University of Paraíba (Opinion No. 1128.0.133.00005) subject to the guidelines of Resolution 196/96 of the National Health Council.

Results

Table I presents the socioeconomic and demographic profile of the children studied. The proportion

Table I
Distribution of children 6-59 months of age according to demographic and socioeconomic variables. Paraiba, 2007

Variables	*N*	*%*
Age group (months)		
≥ 6 e < 24	32	32.0
≥ 24 e < 48	44	44.0
≥ 48 e ≤ 59	23	23.0
Total	100	100.0
Per capita income (MW)[#]		
< ¼	51	51.0
≥ ¼ e < ½	34	34.0
≥ ½	15	14.0
Total	100	100.0
Schooling of the children's responsibles		
Illiterate	15	15.0
Incomplete Elementary School	43	43.0
Elementary school completed	13	13.0
Incomplete high school	06	6.0
Complete High School	19	19.0
Higher Education	–	–
No Information	03	3.0
Total	100	100.0

[#]MW: Minimum Wage = R$ 350.00.

of children between 24 and 47 months was 44.0%. Regarding the income, it was observed that 85.8% of the families studied were below the poverty line, with per capita income less than ½ of the time minimum wage (R$ 350.00). Based on education, it was found that most heads of households (85.8%) attended at most elementary school.

Table II shows that from the biochemical, hematological and hematimetric indicators in study, only the HCM had different mean (SD) according to sex, and the female children had significantly higher concentrations than the male sex, with values of 25.59 pg (± 3.17) and 24.36 pg (± 2.85), respectively (p = 0.045).

Table II
Mean (SD) of the biochemical, hematological and hematimetric parameters according to the children sex. Paraiba, 2007

Variables Mean (DP)	*Sex*		*p*
	Male (n = 50)	*Female (n = 50)*	
Biochemical indicators			
Serum retinol (µmol/L)	0.82 (0.34)	0.82 (0.23)	0.959
Serum iron (µg/dL)	54.35 (28.11)	62.77 (27.78)	0.139
Serum ferritin (µg/L)	21.05 (13.62)	20.87 (14.16)	0.949
Hematological indicators			
Hemoglobin (g/dL)	11.21(1.14)	11.30 (1.85)	0.722
Erythrocytes (million/mm^3)	4.56 (0.41)	4.44 (0.18)	0.149
Hematocrit (%)	34.62 (2.94)	34.64 (4.14)	0.975
Hematimetric indicators			
MCV (fL)	75.45 (45.75)	78.07 (41.22)	0.052
MCH (pg)	24.36 (2.85)	25.59 (3.17)	**0.045**
MCHC (g/dL)	32.25 (1.38)	32.87 (2.95)	0.178
RDW (%)	15.68 (2.08)	14.88 (1.97)	0.052

The mean values (SD) of serum iron, hemoglobin, MCV, MCH, MCHC were statistically higher in children with increasing age (p < 0.05), whereas ferritin and RDW were lower in these children (p < 0.05). There was no statistically significant difference in mean (SD) serum retinol, hemoglobin and hematocrit in children according to age (p > 0.05) (table III).

The comparative analysis of the parameters of iron nutritional status among children with and without VAD indicated that, children with vitamin deficiency had mean values (SD) of serum iron statistically lower than those without vitamin deficiency (p = 0.015). The

Table III
Mean (SD) of the biochemical, hematological and hematimetric parameters according to age group of children. Paraiba, 2007

Variables Mean (DP)	*Age group (months)*			*p*
	6-24 (n = 32)	*24-48 (n = 44)*	*48-59 (n = 24)*	
Biochemical indicators				
Serum retinol (µmol/L)	0.82 (0.32)	0.76 (0.25)	0.90 (0.31)	0.167
Serum iron (µg/dL)	48.22 (25.15)	61.07 (29.17)	67.61 (27.38)	**0.029**
Serum ferritin (µg/L)	17.11 (13.59)	19.43 (12.19)	29.23 (14.18)	**0.002**
Hematological indicators				
Hemoglobin (g/dL)	10.53 (1.39)	11.53 (1.09)	11.74 (0.81)	**< 0.001**
Erythrocytes (million/mm^3)	4.47 (0.35)	4.58 (0.39)	4.41 (0.55)	0.259
Hematocrit (%)	32.82 (3.39)	35.44 (2.95)	34.09 (7.68)	0.052
Hematimetric indicators				
MCV (fL)	73.47 (6.17)	77.01 (6.59)	80.67 (5.39)	**< 0.001**
MCH (pg)	23.50 (2.72)	25.03 (2.78)	26.86 (2.78)	**< 0.001**
MCHC (g/dL)	31.92 (1.46)	32.39 (1.22)	33.71 (3.93)	**0.012**
RDW (%)	15.99 (2.00)	15.36 (2.26)	14.15 (1.15)	**0.003**

Table IV
Mean (SD) of the biochemical, hematological and hematimetric parameters of the nutritional status of iron in the presence of VAD. Paraiba, 2007

Variables Mean (DP)	VDA		p
	Present (retinol < 0,70 mmol/L) (n = 50)	Absent (retinol ≥ 0,70 mmol/L) (n = 50)	
Biochemical indicators			
Serum iron (µg/dL)	51.39 (25.68)	65.06 (29.21)	**0.015**
Serum ferritin (µg/L)	19.89 (13.44)	21.97 (14.22)	0.456
Hematological indicators			
Hemoglobin (g/dL)	11.15 (1.35)	11.36 (1.14)	0.421
Erythrocytes (million/mm^3)	4.43 (0.46)	4.57 (0.37)	0.093
Hematocrit (%)	34.14 (4.01)	34.40 (5.29)	0.783
Hematimetric indicators			
MCV (fL)	76.62 (7.49)	76.82 (5.92)	0.885
MCH (pg)	25.04 (3.61)	24.88 (2.47)	0.800
MCHC (g/dL)	32.62 (2.95)	32.48 (1.45)	0.769
RDW (%)	15.35 (4.88)	15.22 (3.78)	0.766

values of other biochemical, hematology and hemati metric markers of the iron analyzed in this study were not statistically different according to the presence/ absence of VAD (p > 0.05) (table IV).

In table V, it was conducted a multivariate analysis to evaluate the association measures of biochemical, hematology and hematimetric markers of iron nutritional status according to the presence of VAD. It was observed that the serum iron remained the only variable statistically associated with VAD (p = 0.024). Children with VAD had more chance of occurrence of inadequate mean levels of serum iron compared those without VDA (OR = 0.98; CI 95% 0.97-0.99).

Table V
Association measures of biochemical, hematological and hematimetric markers of iron nutritional status on the presence of DVA. Paraiba, 2007

Variables	OR1	CI 95%	p
Biochemical indicators			
Serum iron			
- Normal (≥ 50.0 µg/dL)	1.00		
- Altered (< 50.0 µg/dL)	0.98	0.97-0.99	**0.024**
Serum ferritin			
- Normal (≥ 14.0 µg/L)	1.00		
- Altered (< 14.0 µg/L)	0.99	0.96-1.02	0.386
Hematological indicators			
Hemoglobin			
- Normal (≥ 11.0 g/dL)	1.00		
- Altered (< 11.0 g/dL)	0.83	0.58-1.20	0.935
Erythrocytes			
- Normal (4.60-4.80 million/mm^3)	1.00		
- Altered (< 4.60 e > 4.80 million/mm^3)	0.40	0.14-1.10	0.077
Hematocrit			
- Normal (34.0-42.0 %)	1.00		
- Altered (< 34.0 e > 42.0 %)	0.98	0.90-1.07	0.598
Hematimetric indicators			
MCV			
- Normal (82.0-92.0 fL)	1.00		
- Altered (< 82.0 e > 92.0 fL)	0.99	0.93-1.06	0.907
MCH			
- Normal (27.0-32.0 pg)	1.00		
- Altered (< 27.0 e > 32.0 pg)	1.03	0.89-1.20	0.680
MCHC			
- Normal (30.0-35.0 g/dL)	1.00		
- Alterada (< 30.0 e > 35.0 g/dL)	1.05	0.87-1.26	0.610
RDW			
- Normal (11.0-15.0 %)	1.00		
- Altered (< 11.0 e > 15.0 %)	1.02	0.83-1.26	0.873

[1]OR adjusted for sex and age.

Discussion

The deficiencies of vitamin A and iron constitute a public health problem in Brazil, mainly in the Northeast, where the socioeconomic difficulties contribute significantly to the increase of these nutritional deficiencies in population.[3,18,19]

Most of the families studied presented low levels of income and schooling. The low socioeconomic profile of the population makes difficult the access to goods and services which are essential to maintaining the individual health such as food, shelter and sanitation, creating a favorable environment for the development of nutritional deficiencies and the acquisition of infection and/or infestations.[13,20]

The association between sex and the means of serum retinol of children showed no statistical significance (p = 0.959); being these results that corroborate studies conducted in the states of Piauí[8] and Bahia.[21]

Some studies also indicate a higher incidence of anemia in male children, a fact that may be related to a higher growth rate compared to female children, which leads to an increased need for iron by the organism.[22] However, the comparison of hemoglobin means by sex presented in this study did not indicate statistical significance (p = 0.722). These results are consistent with studies in Paraíba[23] and Santa Catarina.[24] Among the biochemical, hematological and erythrocyte indicators of the iron nutritional status evaluated, only the MCH showed statistically different in male and female children (p = 0.045).

With regard to the age distribution and the retinol, it was not confirmed the trend observed in certain studies that younger children tend to have lower level of serum retinol.[8,21] The results of this study are consistent with those found in a study conducted with children from São Paulo.[25]

However, there was a statistically significant difference in hemoglobin of children with different age groups (p < 0.001). The hemoglobin levels were higher in children of older age, with the peak of

anemia observed in younger children, located between the ages of 6 to 24 months. Similar results were found in studies performed in Pernambuco[26] and São Paulo.[27] The values of serum iron, MCV and MCHC also increased with advancing age of the children ($p < 0.05$), unlike serum ferritin and RDW, whose rates were reduced ($p < 0.05$).

The high prevalence of anemia at the age of 6 to 24 months may be related to the fact that this is a period of rapid physical growth, and there is consequently an increase in iron requirements. On the other hand, it is also possible that anemia in these children has been manifested in the first year of life, due to early weaning and/or delay to the introduction of iron-rich foods. The decrease in the rate of growth and gradual evolution of a diet mainly of milk for a more varied diet, rich in food sources of iron contribute to a decrease in prevalence of anemia among children of higher age.[26,28]

The comparison of the nutritional status of iron according to the presence of VAD showed significant difference only in the values of serum iron ($p = 0.015$), with iron levels higher in the absence of VAD. These findings corroborate the results from studies obtained with children in Brazil,[29,30] Canada[31] and Thailand.[32] In the present study, no association was found between VAD and ferritin, a phenomenon described in other studies.[31,33]

Anemia caused by vitamin A deficiency, unlike iron deficiency anemia, characterizes by presenting serum ferritin levels within the normal range and changed serum iron levels.[12] In this study, children with VAD had mean (SD) serum ferritin 19.89 µg/L (± 13.44), higher than the reference value (14 µg/L),[15] whereas the mean (SD) serum iron of 45.00 µg/L (± 25.68) was lower than the reference value (50 µg/L).[15] In cases of anemia caused by vitamin A deficiency, functional iron deficiency may develop even when stocks of this mineral are present.[12] This phenomenon can be explained by the fact that the VAD: 1) compromise the mobilization of iron stores, resulting in insufficient concentrations to the bone marrow, so as to impair erythropoiesis, 2) make the body more susceptible to the infection processes, which cause increasing concentrations of ferritin and reduced concentrations of transferrin, and 3) erythropoietic damage by interfering in the synthesis of eritropoetina.[6,12,13]

Thus, the interaction between iron deficiency and vitamin A observed in several studies was reinforced in this study only in relation to the deficit of circulating iron (serum iron), but not to iron stores (serum ferritin) and anemia itself, suggesting a failure in the transport mechanisms of the mineral in children with VAD. These findings suggest the need to intensify joint efforts to fight these nutritional deficiencies, in order to reduce the prevalence of such deficiencies and to intercede on the interaction between the two most common nutritional deficiencies on a global scale.

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