Original Articles DOI: 10.1590/S0034-8910.201304702906

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Vitamin A deficiency and associated factors in children in urban areas

ABSTRACT

OBJECTIVE: To estimate the prevalence of vitamin A deficiency and its associated factors in children.

METHODS: A cross-sectional population-based study, involving 1,211 children of both sexes, aged between six and 59 months old, was carried out in the urban zone of 9 cities in the state of Paraiba, Northeastern Brazil. Vitamin A status was assessed by serum retinol levels (high performance liquid chromatography – HPLC) and subclinical infection was assessed by C-reactive protein concentrations. Socioeconomic, demographic and sanitation conditions, as well as vitamin A supplement intake, were also evaluated. Children with serum retinol concentrations

RESULTS: The prevalence of vitamin A deficiency was 21.8% (95%CI 19.6;24.2), showing an association with subclinical infection and lack of indoor plumbing. The prevalence of vitamin A deficiency was 21.8% (95%CI 19.6;24.2). After adjustment, vitamin A deficiency was found to be linked with subclinical infection and lack of indoor plumbing. Vitamin A deficiency was four times higher (CI95% 1.49;10.16) in children with subclinical infection whose homes were without indoor plumbing, compared to children who were not infected and with indoor plumbing in their homes.

CONCLUSIONS: Despite activities aimed at the prevention and control of vitamin A deficiency, hypovitaminosis A, remains a public health concern among children under five.

DESCRIPTORS: Infant. Child, Preschool. Vitamin A Deficiency, epidemiology. Risk Factors. Socioeconomic Factors. Cross-Sectional Studies.

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Received: 10/12/2010
Approved: 9/9/2012

Article available from: www.scielo.br/rsp

INTRODUCTION

Vitamin A is a micronutrient known to be related to visual functions, epithelial integrity and the functioning of the immune system. Studies indicate that vitamin A deficiency (VAD) is a public health problem in the Northeast and North and in some regions of the Southeast of Brazil.[8,9,12,15,17,a,b]

In the state of Paraiba, this deficiency has been recognized since the 1980s.[3] Results of a clinical-nutritional study carried out in three regions of this state, between 1981 and 1982, show a high prevalence of Bitot's spots and corneal scars in children in the *sertão* (desert region), especially in periods between harvests.[16] Cases of corneal xerophthalmia (ulcer/queratomalacia) have also been documented in children in João Pessoa.[1] In the following years, clinical manifestations of moderate xerophtalmia and corneal scars, were also observed in children aged between two and 28 months, mainly during the drought which lasted from 1981 to 1984.[4] Approximately a decade later, a 16% prevalence of VAD was found in pre-school children in a population based survey, indicating a moderate public health problem.[a] Since1992 there have been no other population based investigations into this problem in the state.

The main causes of VAD can be divided into two broad categories: malnourishment and the presence of infectious processes. Malnourishment encompasses deficits in intake of Vitamin A rich-food, as well as inadequate consumption of foods containing nutrients important for its absorption. Diet is affected by cultural factors, such as eating habits, individual and family preferences and by socioeconomic factors which affect the capacity to select and buy these foods.[2,c]

Infections can result in reduced serum retinol concentrations in the first 24 hours after onset. The presence of sub-clinical infection may lead to VAD due to reductions in the retinol binding protein,[20] regardless of insufficient intake of food sources and the hepatic reserves of the vitamin. However, episodes of serious or prolonged infection may affect hepatic reserves, due to reduced food intake, lower absorption, increased biological use and abnormal urinary excretion of retinol serum.[7]

Among strategies to prevent and control VAD, international organizations have advocated the massive supplementing of Vitamin A using mega doses for children aged from six to 59 months and in women immediately post-partum, considered to be an emergency intervention, and this has been adopted by the Brazilian Vitamin A Supplement Program. The state of Paraiba was a pioneer in establishing this program in the 1980s. According to Martins et al (2007), this state showed the highest levels of coverage and regularity between 1996 and 1998, compared to other states included in the Program.[10]

Bearing in mind the high prevalence of Vitamin A deficiency in Paraiba found in the 1992 survey and the lack of subsequent studies evaluating trends in this deficiency, the aim of this study was to analyze the prevalence of VAD in children and associated factors.

METHODS

A transversal, population-based study was carried out with children aged six to 59 months old, of both sexes, resident in the urban area of the state of Paraiba between January and March 2007.

The probabilistic sample was calculated based on an estimated 16%[a] (p) prevalence of VAD, the confidence interval (E = 1.96) for a 5% margin of error, sample correction factor of (c) of 2.1, as the sample is based on cluster technique, and accuracy (A) (or margin of error) of 3.0%. Based on the formula $N = [E^2.p(1\text{-}p).c]/A$ the minimum sample was calculated to be 1,204 children. Adding 10% for possible losses, a final sample size of 1,324 children was arrived at. Increasing the sample size (sample correction factor of 2.1) has been recommended by the World Health Organization (WHO)[6] when making estimates about the population of geographical areas such as those in this study, considering the marked climatic diversity that shapes the meso-regions of the state and especially the great heterogeneity in the dynamics of urban space use. Thus, with the sample size more than doubled, design effect was minimized with the correction of potential intra-cluster variations.

The children were randomly selected, according to the two-stage sampling technique, using the municipality (first cluster) and the census tract (second cluster). Thus, nine municipalities located in the *sertão* (desert region) (Belém do Brejo da Cruz, Boa Ventura, Conceição, Malta, Patos, Pedra Branca e São José de Espinhares), the *agreste* (region between the desert and the forest areas) (Campina Grande) and the *zona da mata* (forested) regions (João Pessoa).

[a] Diniz AS. Aspectos clínicos, sub-clínicos e epidemiológicos da hipovitaminose A no estado da Paraíba (tese de doutorado). Recife: Universidade Federal de Pernambuco; 1997.
[b] Instituto Nacional de Alimentação e Nutrição/ Instituto Materno-Infantil de Pernambuco/ Departamento de Nutrição, Universidade Federal de Pernambuco/ Secretaria Estadual de Saúde de Pernambuco. II Pesquisa Estadual de Saúde e Nutrição: saúde, nutrição, alimentação e condições sócio-econômicas no Estado de Pernambuco,1997. Recife; 1998.
[c] World Health Organization. Global prevalence of vitamin A deficiency. MIDIS working paper 2 (WHO/NUT/(95.3). Geneva; 1995.

The municipalities of João Pessoa and Campina Grande were selected beforehand as they possessed population density significantly higher than the other municipalities in the state, and due to their location (municipalities in two of the three bioclimatic zones. Considering that the distribution of the health problem in question may be affected by geographical location, including these regions in the sample, represented by their most densely populated municipalities, helps to reinforce the sample's representativeness. The other seven municipalities were randomly selected from within the *sertão* meso-region, bearing in mind the homogeneity in population density in municipalities in this region.

Using a random number table in the randomization of census tracts and residences, observing the upper limit of 40 sample units per cluster (census tract) also served to include the assumptions necessary for a probabilistic selection of the sample units. Parents and guardians in the selected residences were invited to take part in the study, with a refusal rate of approximately 4% due to refusal or absence. Of the 1,324 children originally selected, 1,211 were studied. Some losses occurred due to collecting insufficient biological material for the biochemical analysis, as well as mothers' refusals to participate. The mean age was 33 months (SD = 15.7 months), and 51.2% of the children were male.

Blood was collected to analyze concentrations of serum retinol and C-reactive protein, and a questionnaire used to collect socioeconomic and demographic data on the study population. The children's health records were used to extract data on previous megadoses of Vitamin A supplement.

The blood was collected between one to three working days after the household interview, in a location close to the subjects' homes, usually the families' primary care center. When it was not possible to use these centers, the blood was collected at parenting groups, churches or residents' associations.

In order to carry out the laboratory tests, the blood samples (5 mL) were collected first thing in the morning, without the need for fasting, using disposable needles and syringes, and were stored in aluminum tubes to protect them from light.

After removal of the coagulant, the blood was centrifuged at a speed of 3,000 rpm and two serum aliquots were stored in amber and transparent eppendorf tubes, to determine the concentrations of serum retinol and C-reactive protein, respectively. The samples from municipalities in the sertão were stored and transported to the laboratories, maintaining the cold chain.

Serum retinol concentrations were measured using high performance liquid chromatography (HPLC), following the technique proposed by Furr et al,[d] Micronutrient Research Center of the *Universidade Federal da Paraíba* (UFPB). C-reactive protein concentrations were assayed using the latex agglutination test in the Biochemistry Laboratory of the *Hospital Universitário Lauro Wanderley*, UFPB.

WHO cutoff points were used to assess retinolemia, according to retinol serum levels, these being: deficient (< 0.35 μmol/L), low (≥ 0.35 μmol/L and < 0.70 μmol/L), acceptable (≥ 0.70 μmol/L and < 1.05 μmol/L) and adequate (≥1.05 μmol/L). Children with serum retinol concentrations < 0.70 μmol/L were considered to have a deficiency. CRP concentrations ≥ 6 mg/L were considered to be cases of subclinical infection.[19]

EpiInfo v.6.04b (WHO/CDC, Atlanta, GE, USA) software was used to create the database, using double data entry for 100% of the data. In order to check the consistency of the data entry, the 'validate' application was used and the Statistical Package for Social Sciences version 13.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

VAD (low or deficient levels of retinol) was a dependent variable, and the independent variables were the socioeconomic and demographic data, previous Vitamin A supplements, the presence of subclinical infection and basic sanitary conditions. The Kolmogorov-Smirnov test was used to assess the assumption of normality of the retinol serum variable, described as mean and standard deviation. Percentages and their respective 95% confidence intervals were described.

To evaluate the difference in the mean concentrations of serum retinol, according to the presence/absence of subclinical infection, the Student's t test for unpaired data was used. The prevalence and odds ratios were adopted, respectively, as measures of occurrence and epidemiological association. Pearson's Chi-squared test was used to assess the statistical significance when comparing percentages. Forward stepwise logistic regression was used for the simultaneous analysis, with the calculation of the adjusted measures, using $p < 0.05$ and $p > 0.10$ as criterion for inclusion and exclusion respectively. The statistical significance of the associations analyzed was based on p value < 0.05.

The test results were sent to the primary health care centers closest to the children's residences, with a letter explain the meaning of the biochemical results, to the health care professionals at the centers. Where this was not possible, the results were sent by mail to the participant's residence, with an explanatory letter for

[d] Furr HC, Tanumiharjo S, Olson JA. Training manual for assessing vitamin A status by use the modified relative dose response assays. Ames: Iowa State University; 1992.

Table 1. Concentration of retinol in children according to presence/absence of infection. Paraiba, Northeastern Brazil, 2007.

Variable	Children with/without subclinical infection (n = 1,211)			Children with subclinical infection (n = 141)			Children without subclinical infection (n = 1,070)		
Retinol levels (μmol/L)	n	%	FA	n	%	FA	n	%	FA
Deficient (< 0,35)	3	0.2	0.2	1	0.7	0.7	2	0.2	0.2
Low (≥ 0,35 e < 0,70)	262	21.6	21.8	52	36.9	37.6	210	19.6	19.8
Acceptable (≥ 0,70 and < 1,05)	652	53.8	75.6	73	51.8	89.4	579	54.1	73.9
Adequate (≥ 1,05)	294	24.4	100.0	15	10.6	100.0	279	26.1	100.0
Mean (μmol/L)		0.90			0.80			0.91	
Standard deviation		0.24			0.23			0.24	

AF: Accumulated Frequency

the child's mother. In cases where VAD was detected, the mother was advised to seek assistance in the nearest primary health care center.

The research protocol was approved by the Committee for Ethical Research of the *Universidade Estadual da Paraíba* (protocol nº 1128.0.133.000-05 in 20/12/2005).

RESULTS

There was a 21.8% (95%CI 19.6;24.2) prevalence of VAD deficiency (< 0.70 μmol/L). The majority of the children (53.8%; 95%CI 51.0;56.6) had acceptable retinol serum levels (≥ 1.05 μmol/L). Subclinical infections were present in 11.6% of the children % (95%CI 9.8;13.4). Retinol serum concentrations were significantly lower in children with subclinical infections compared with those without infection ($p < 0.001$) (Table 1).

Table 2 shows the prevalence of VAD according to the variables studied. Only the presence of a subclinical infection proved to be significantly linked to VAD. The prevalence of VAD (37.6%, 95%CI 29.6;45.6) among children with subclinical infection was higher ($p < 0.001$) than those with no infection (19.8%, 95%CI 17.4;22.2). The variables: number of people in the household and indoor plumbing showed results bordering on statistically significant. There was no observed link between VAD and Vitamin A supplements in the previous six months ($p = 0.77$).

After adjusting the model in the logistic regression analysis, the variables subclinical infection ($p < 0.01$) and indoor plumbing ($p = 0.02$) remained in the model, characterized as the best predictors of VAD. The presence of subclinical infection proved to be a risk factor associated with VAD and indoor plumbing as a protection factor against vitamin A deficiency. VAD was four times more likely to occur (95%CI 1.49;10.16) in children with a subclinical infection and without indoor plumbing in their home, compared with those with no infection living in a house with indoor plumbing (Table 3).

DISCUSSION

The 21.8% prevalence of VAD can be considered as a serious public health problem, according to WHO criteria.[e] High prevalence of VAD have been found in representative samples of children under 5 in other states in the Northeast of Brazil, such as Pernambuco (22.3%),[b] Alagoas (44.8%),[21] Bahia (44.7%)[12] and Sergipe (32.1%).[9] According to the National Demographic and Health Survey 17.4% of children have VAD, with the highest rates of prevalence found in the Northeast (19.0%) and Southeast (21.6%) of the country.[f]

Both insufficient dietary intake of Vitamin A and infections lead to reduced levels of retinol in the blood, although they are situations requiring different solutions, depending on the nutritional status. In the case of the former, there is a reduction in the hepatic reserves. In the latter, vitamin A stored in the liver may well be at normal levels, it being the transport of Vitamin A which is affected as a result of reduced synthesis of the retinol binding protein as a consequence of the infection process. This means it is necessary to verify whether the vitamin A deficiency is due to insufficient intake

[e] World Health Organization. Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating interventions programs. Geneva: WHO; 1996.
[f] Ministério da Saúde; Centro Brasileiro de Análise e Planejamento. Pesquisa Nacional de Demografia e Saúde da Criança e da Mulher – PNDS 2006: dimensões do processo reprodutivo e da saúde da criança. Brasília (DF); 2009. (Série G. Estatística e Informação em Saúde).

Table 2. Prevalence and odds ratio for risk of Vitamin A deficiency, according to the variables in the study, in children in Paraiba, Northeastern Brazil, 2007.

Variable		Prevalence of VAD (retinol serum < 0.70 µmol/L)		OR	IC95%
	n	n	%		
Age (months)					
6-11	125	38	30.4	1	-
12-23	281	57	20.3	0.58	0.36;0.94
24-35	248	55	22.2	0.65	0.40;1.06
36-47	281	62	22.1	0.65	0.40;1.04
48-59	276	53	19.2	0.54	0.33;0.88
Sex					
Male	620	137	22.1	1	-
Female	591	128	21.7	0.97	0.74;1.28
Vitamin A supplement (in the last 6 months)					
No	745	165	22.1	1	-
Yes	466	100	21.5	0.96	0.72;1.27
Subclinical infection (C-reactive protein -CRP)					
< 6 mg/dl	1,070	212	19.8	1	-
≥ 6 mg/dl	141	53	37.6	2.44	1.68;3.54
Mother's age (years)					
15-19	113	23	20.3	1	-
20-24	348	83	23.8	1.22	0.73;2.06
25-29	318	75	23.6	1.21	0.71;2.04
30-34	186	40	21.5	1.07	0.60;1.91
35-54	229	40	17.5	0.83	0.47;1.47
Mother's schooling (years in school)					
≤ 5	384	77	20.0	1	-
6-9	409	103	25.2	1.34	0.96;1.88
≥ 10	399	82	20.5	1.03	0.73;1.46
Head of household schooling (years in school)					
≤ 5	585	127	21.7	1	-
6-9	290	63	21.7	1.00	0.71;1.41
≥ 10	325	72	22.1	1.03	0.74;1.42
Head of household work					
Unemployed	161	39	24.2	1	-
Formally employed	472	104	22.0	0.88	0.58;1.35
Casually employed	423	89	21.0	0.83	0.54;1.28
Other	153	33	21.6	0.86	0.51;1.46
Household income *per capita* (MS)[a]					
≤ 0.25	517	129	24.9	1	-
> 0.25 e ≤ 0.5	435	87	20.0	0.75	0.55;1.02

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> 0.5	237	46	19.4	0.72	0.50;1.06
Type of house (construction)					
Brick	1,042	226	21.7	1	-
Other	168	39	23.2	1.10	0.74;1.61
Number of rooms in the home					
1-4	407	101	24.8	1	-
5 or more	801	164	20.4	0.78	0.59;1.03
Number of household members					
< 7	943	195	20.7	1	-
7 or more	267	70	26.2	1.36	0.99;1.87
Indoor plumbing					
No	162	45	27.8	1	-
Yes	1,048	219	20.9	0.69	0.47;1.00
Garbage collection					
Other	59	16	27.1	1	-
Public network	1,151	248	21.5	0.74	0.41;1.33
Sewer					
Other	181	39	21.5	1	-
Public network	1,030	226	21.9	1.02	0.70;1.50

MS: minimum salary = R$ 350 (R$ 1 equivalent to US$ 2,133)
VAD: vitamin A deficiency

or whether it is a secondary response to an infection.[20] Food intake was not assessed in this study, which can be considered a limitation.

Based on the VAD prevalence of 21.8% in the total population of the study and 19.8% in children without infections, a 2.0% reduction can be observed, highlighting the influence of infection on the Vitamin A nutritional status. Corroborating these findings, Wieringa et al[23] (2002) observed an overestimation of the prevalence of VAD of around 4.6% comparing prevalence

Table 3. Odds ratio adjusted for risk of vitamin A deficiency among children according to infection status and indoor plumbing in the home. Paraiba, Northeastern Brazil, 2007.

Variable	Vitamin A deficiency (retinol serum < 0.70 μmol/L)	
	Adjusted OR[a]	95%CI
Subclinical infection		
No	1	–
Yes	2.55	1.74;3.75
Indoor plumbing		
No	1	–
Yes	0.65	0.45;0.96
Water - infection		
Indoor plumbing and no subclinical infection	1	–
Indoor plumbing and presence of subclinical infection	1.29	1.71;3.92
No indoor plumbing and no subclinical infection	1.56	1.03;2.37
No indoor plumbing and presence of subclinical infection	3.86	1.49;10.16

[a]Adjusting for age, sex, vitamin A supplement in the last six months, mother's age, mother's schooling, head of household schooling, *per capita* income, household type, number of rooms and people in the household, garbage and sewage type.

among children with and without infection, assessed by C-reactive protein and α1-acid glycoprotein concentrations. Thurnham et al[19] (2003) observed a reduction from 20% to 16% prevalence of VAD in children under 5 compared with estimates for the total population, obtained after correcting to remove the influence of inflammatory activity on retinol serum concentrations.

No link was observed between VAD and socioeconomic and demographic data. According to Ramalho et al,[14] deficiencies in micronutrients may manifest themselves regardless of economic conditions, as they are also a result of inappropriate dietary habits related to specific cultural patterns. With regards to age group, the homogeneous behavior of VAD prevalence in the children in this study does not confirm a trend observed in other studies with pre-school children, in which younger children showed lower levels of serum retinol.[17,22] These children's eating habits are characterized by diets of diluted milk and high percentages of carbohydrates. These eating habits, together with early weaning and reduced consumption of food sources of carotenoids, may explain the insufficient retinol serum levels in children in lower age groups.[12] In this study, no statistical differences with regards to VAD and the children's gender were found, a result similar to those observed in other studies.[5,12,22] According to the WHO,[c] differences in rates of VAD prevalence related to sex are attributed to cultural differences in eating habits and are not consistent with the existence of a physiological factor in this association.

In this study, statistically significant correlation between serum retinol and C-reactive protein levels were observed, indicating that the presence of subclinical infection increases the chance of a child having VAD by 2.55 times. A meta-analysis of the effect of subclinical infection on retinol serum levels, identified significantly higher retinol values in individuals with normal C-reactive protein levels, showing the damage inflammatory processes have on the Vitamin A nutritional status.[19] Moreover, in mild infections the reduction in retinol serum, due to inflammatory processes, may have a transient effect on cases of changes in the metabolizing of vitamin A, not accompanied by reduced hepatic stores. However, in the case of serious or prolonged infections, this alteration may affect hepatic Vitamin A stores, aggravating the deficiency still further.[7]

The increased susceptibility of children in homes without indoor plumbing to VAD shows the importance of environmental factors in determining deficiency. It is assumed that, in addition to infectious processes, economic and structural factors may aggravate the occurrence of VAD. According to the WHO,[c] a water supply insufficient for drinking, personal hygiene and growing food is among the factors associated with malnutrition, including VAD, and explaining the risk of VAD associated with lack of indoor plumbing in the home.

The synergy between nutritional problems and infections, especially in unsanitary conditions, establishes a vicious circle resulting in varying degrees of retarded growth and development in children which needs to be reversed.[18] Analyzing the water-infection variable, the importance of contributing factors to the occurrence of VAD can be observed, such as the high prevalence of infections, lack of sanitation and drinking water, as well as adverse socioeconomic conditions and taboos related to food of plant origin which increase the demand or interfere in the organism's intake and metabolizing of Vitamin A.[13]

The results of this study show that, in spite of actions to prevent and control VAD on the part of the state of Paraíba, it is still a serious public health problem, demanding specialist attention from the government organizations which deal the population's health and nutrition. In this context, it is necessary to consider the importance of concerted actions covering sanitation, immunization and the control of diarrheal and parasitic diseases as a form of preventing and controlling Vitamin A deficiency.

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The authors declare that there are no conflicts of interests.