ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 11, Issue, 11, pp. 51898-51902, November, 2021
https://doi.org/10.37118/ijdr.23303.11.2021

RESEARCH ARTICLE OPEN ACCESS

CHARACTERIZATION OF ANEMIA AND ASSOCIATION WITH SUBCLINICAL INFECTION IN CHILDREN FROM RURAL AREAS OF THE NORTHEAST OF BRAZIL

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ARTICLE INFO

Article History:
Received 15th August, 2021
Received in revised form
16th September, 2021
Accepted 10th October, 2021
Published online 28th November, 2021

Key Words:
Anemia, Children, C-Reactive Protein, Infection.

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ABSTRACT

Anemia is the most prevalent nutritional deficiency worldwide.It is considered a public health problem that is related to iron and infectious process. This study aimed at characterizing anemia and relating it to subclinical infection in children under the age of five years old residing in rural areas of Teresina, in Piauí state. A subsample of 103 children from 6 to 59 months, from both sexeswas evaluated. In order to diagnose anemia, a concentration of hemoglobin was used, and children were considered anemic when the values were smaller than 11mg/dL. In order to characterize and classify the anemia present in the population, red blood cell indices were used, considering as iron deficiency anemia the limits below normality for: Mean corpuscular volume - MCV (72fl), Mean corpuscular hemoglobin - MCH (24pg) and *Red Cell Distribution Width* - RDW>14.5%. The value of C-reactive protein > 5mg/L was considered an indication of the presence of infection or inflammatory process. The prevalence rates of anemia and subclinical infection were 25.7% and 7.7%, with no significant association between the red blood cell indices and this characteristic. The alterations in the red blood cell indices were useful to classify it as iron deficiency anemia.

Citation: ***Maria da Cruz Moura e Silva, Ayla Patrícia Soares do Nascimento, Lívia Patrícia Rodrigues Batista et al.*** "Characterization of anemia and association with subclinical infection in children from rural areas of the northeast of Brazil", *International Journal of Development Research*, 11, (11), 51898-51902.

INTRODUCTION

Anemia is considered the most prevalent nutritional deficiency all over the world, despite the epidemiological changes observed in the last few years. It is a public health problem that affects, above all, developed and emerging countries (Oliveira *et al*. 2013). The World Health Organization (WHO) estimated that anemia reaches 54.9% of children in pre-school age in Brazil, and most regional findings point out to rates above 40% (Rocha *et al*. 2012).

There are segments of the population that are more vulnerable to nutritional anemia, since they are in food insecurity situations, such as those who live in rural settlements, especially children. Scopinho (2010) identified some of the factors that debilitate this population group, among them the lack of basic sanitation, poor living conditions and lack of infrastructure regarding transportation, roads, education, health assistance and electric energy. Regarding the anemia diagnosis, it can be defined by the level of hemoglobin circulating in the blood, and this has been the universally adopted parameter.

However, such parameter is not sensitive enough to evaluate iron deficiency due to the variation in hemoglobin concentration according to sex, age, ethnic group, among other factors (Carvalho *et al*. 2010). Thus, the red blood cell indices (mean corpuscular volume - MCV; mean corpuscular hemoglobin - MCH; mean corpuscular hemoglobin concentration - MCHC; red cell distribution width - RDW) have been used to minimize this problem and make the anemia diagnosis clearer (Paiva *et al*. 2000; Naoum 2011). Iron has several roles in the body, among them the transportation and storage of oxygen molecules such as hemoglobin and myoglobin, as well as enzymes required for the generation of energy and production of intermediate metabolites essential to the immune system (Lemos *et al*. 2010). Therefore, its deficiency may determine loss of resistance to infections and disorders that may be irreversible, even with an appropriate treatment (Morgan and Sperotto 2011). During the acute phase response in infectious processes, the plasma concentrations of several micronutrients are altered. The C-reactive protein concentration (CRP) in plasma increases rapidly, so it is an important indicator of subclinical infection. Regarding iron, there are alterations in the functions of transportation and storage, which explains a reduction in the concentrations of this mineral in infections (Wieringa *et al*. 2002; Sales *et al*. 2011). Therefore, since anemia is a relevant public health problem and considering the importance of the relationship between iron and the infectious process, this study intends to characterize anemia and relate it to subclinical infection in children under the age of five residing in rural areas of Teresina-PI.

MATERIALS AND METHODS

This study is a cutout from a wider research entitled "Food insecurity and anemia in children under five years old in settlements from Teresina, Piauí", with the objective of investigating the prevalence of food insecurity and anemia, as well as the associated factors in this population. It is a quantitative, cross-sectional study, with a descriptive and analytical focus, carried out in homes from the Settlement Projects (Projetos de Assentamentos - PA) from InstitutoNacional de Colonização e ReformaAgrária (INCRA) in the city of Teresina, Piauí. The data collection was done in 2013.

PARTICIPANTS AND SAMPLES: 131 children from the original project, under five years of age, from both sexes, participated, representing all children in this age group residing in rural settlements from Teresina. For the present study, we worked with a subsample of 103 children from 6 to 59 months of age, which had blood tests and CRP dosage.

SOCIOECONOMIC AND DEMOGRAPHIC DATA COLLECTION: The socioeconomic and demographic data was raised through the application of a form to one of the family heads, covering issues related to the economic and demographic conditions: school level of the people responsible for the children, mother's age, family income and per capita income, as well as participation in government programs of income transfer.

DIAGNOSIS AND CHARACTERIZATION OF ANEMIA: In order to diagnose anemia, a concentration of hemoglobin (Hb) was used, and children were considered anemic when the Hb values were < 11.0 mg/dL (WHO 2008). In order to characterize and classify the type of anemia present in the population, red blood cell indices were used, considering as iron deficiency anemia, besides reduced Hb, the limits below normality for MCV - 72fl, MCH - 24 pg and RDW > 14.5%, which is suggested for the diagnosis of iron deficiency (Hadler 2002). The complete blood count was done in a XS-1000i SysmexTM automatic counter and blood smears, colored with a fast Panoptic kit, for the morphological analyses of erythrocytes; for that, 2 mL of Peripheral venous blood was collected in the settlements, in the morning, by a technician in a laboratory, under the supervision of the study researchers. The blood samples were deposited in tubes with EDTA anticoagulant. The analyses were carried out in the Clinical Analyses Laboratory from the University Hospital at the Federal University of Piauí (HU-UFPI).

DETERMINATION OF C-REACTIVE PROTEIN – CRP: The CRP samples were determined in the Clinical Analyses Laboratory from the HU-UFPI, according to the immunoturbidimetric method, through a COBAS INTEGRA PLUS 400 (*Roche® Diagnostics*, Brasil) automatic biochemical analyzer, by using the C-reactive protein cassette kit – *Roche®* The value of CRP > 5 mg/L was considered an indication of the presence of infection or inflammatory process (Thurnham *et al*. 2003).

DATA ANALYSIS: The statistical analyses were developed through softwares *Statistical Package for the Social Sciences* (SPSS), Windows 20.0 version, and *Bio stat* 5.0 version. In order to characterize the study population, a descriptive analysis with frequency measurements, central tendency and dispersion was used.
In order to compare the averages among groups, the variables were tested as to their normality by the Kolmogorov-Smirnov test; those with normal distribution were analyzed by the *Student* t test and ANOVA, followed by the Tuckey test, in order to check the groups that differ from each other; those that did not present normal distribution (CRP and RDW), the Mann Whitney and Kruskal Wallis tests were used, followed by the Dunn test, in order to investigate the groups that differ from each other. The statistical analyses were done considering the statistical significance level of $p < 0.05$.

ETHICAL ASPECTS: The study was carried out according to the ethical legislation in research for human beings (Resolution 466/2012, National Health Board 2012), and it has been approved by the UFPI Ethics Research Committee, approval no. 383.869. The people responsible for the children participating in the study signed the form of consent and agreement with the research. Children old enough to understand the research (from 12 months on) also signed the Free and Clarified Consent Term. The blood cell count report was delivered to one of the people responsible for the child, and this person was instructed to go to the closest UnidadeBásica de Saúde (Basic Health Unit).

RESULTS

Table 1 shows the sociodemographic characteristics of the population studied. From the 103 children studied, 54.2% were female, with prevalence (40.56%) of the age group from 24 to 48 months of age.

Table 1. Characterization of the sample according to socioeconomic and demographic variables.Teresina, Piauí, 2013

Variables	N	%
Children age (months)		
6 to 24	36	35.6
24 to 48	41	40.6
48 to 59	24	23.8
Sex		
Female	55	54.5
Male	46	45.5
Mother's age (years)		
< 20	6	6.2
20 to 29	65	67.0
≥ 30	26	26.8
Father school level (years of study)		
0	9	9.8
1 to 4	24	26.1
5 to 8	30	32.6
≥ 9	29	31.5
Family income (MW)*		
< 1	33	32.7
1 to 2	55	54.5
> 2	13	12.9
Bolsa Família (Governmentbonusprogram)		
Yes	73	72.3
No	28	27.7

*MW= Minimum wage (R$ 678,00)

Most (67%) mothers were between 20 and 29 years old, and 45.4% of them had 5 to 8 years of study, same amount of years the fathers had. Most of the families (72.3%) were beneficiaries of the BolsaFamília

(Government bonus program), and more than half, 54.5%, of the families had an income of 1 to 2 minimum wages. Analyzing the anemia diagnosis in the child population, a prevalence of 25.7% of anemia (n=27) (hemoglobin < 11 g/dl) was observed. Among the children with anemia, there was mild predominance, in which 85.19% of the children presented concentrations of Hb< 11.0 and > 9.0 g/dl. The highlight is that there were no cases of serious anemia (Hb< 7.0 g/dl). There was no association between anemia and sex (p = 0.169) (Table 2).

Table 2. Prevalence of anemia according to the distribution by gender in children from 6 to 59. Teresina, Piauí, 2013.

Presence of anemia	Prevalence N (%)	
	Female	Male
Yes	14 (51.9%)	13 (48.1%)
No	44 (56.4%)	34 (43.6%)
Total	58 (55.2%)	47 (44.8%)

p= 0.169 (p value of the Pearson chi-square)

The values of hemoglobin varied in the studied population, with a minimum concentration of 8.1 g/dl and maximum of 14.5 g/dl, with an average concentration of 11.4 ± 1.2 g/dl. According to the age group, values of hemoglobin below the minimum acceptable by WHO were observed in the age groups of 06 to 24 months, and the age groups of 25 to 59 months presented this parameter within normality according to the stratification of groups per age. Tables 3 and 4 bring the haematological parameters and their variations among the groups of anemic and non-anemic, as well as their relationship to the sex and age of the children. Regarding the sex, there was no significant difference among the parameters evaluated.

Table 3. Clinical parameters and their variations according to the children's sex Teresina, Piauí, 2013

Clinical Parameters	Sex		p
	Female (M ± DP)	Male (M ± DP)	
Hb (g/dL)	11.49 ±1.056	11.32 ±1.301	0.456
VCM (fl)	76.59 ±6.001	74.05 ±6.378	0.042
HCM (pg)	25.78 ±2.512	24.66 ±2.701	0.034
CHCM (g/dL)	33.60 ±1.254	33.19 ±1.348	0.120
RDW (%)	13.64 ±3.869	14.30 ±3.743	0.159*
PCR (g/dL)	2.15 ±5.992	1.19 ±3.112	0.852*

Mean (M), Standard Deviation (SD) and p value according to the *Student* t test (significance level = 0.05) of the parameters: hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), C-reactive protein (CRP). * p-value referent to the Mann-Whitney test.

The means of Hb, MCV, MCH, MCHC and RDW values, according to the age groups, differed significantly from each other. However, the MCH and MCHC parameters presented statistically different variances (Levene's test, $p \leq 0,05$), and it cannot be affirmed accurately that the means differ. There was statistical difference in Hb, MCV, MCH and RDW between the group ages from 6 to 24 months and 24 to 48 months. There were no differences between any parameter when comparing the age groups of 24 to 48 months with 48 to 59 months. There was significant difference in Hb, MCV, MCH and RDW between the groups of 6 to 24 months and 48 to 59 months (Table 4).

Table 4. Clinical parameters and their variations according to the children's age. Teresina, Piauí, 2013

Clinical Parameters	Age (months)			p
	6 to 24 (M ± DP)	24 to 48 (M ± DP)	48 to 59 (M ± DP)	
Hb (g/dL)	10.83 ± 1.295[ab]	11.64 ± 1.053[a]	11.89 ± 0.790[b]	< 0.001
VCM (fl)	71.84 ± 6.673[ab]	76.72 ± 4.954[a]	78.61 ± 5.196[b]	< 0.001
HCM (pg)	23.76 ± 2.946[ab]	25.66 ± 1.900[a]	26.88 ± 2.103[b]	< 0.001
CHCM (g/dL)	33.00 ± 1.562[a]	33.38 ± 0.955	34.10 ± 1.165[a]	0.005
RDW (%)	15.83 ± 2.686[ab]	13.39 ± 3.311 [a]	12.04 ± 4.801 [b]	<0.001*
PCR (g/dL)	1.94 ± 6.305	1.89 ± 4.261	1.07 ± 3.407	0.511*

Mean (M), Standard Deviation (SD) and p value according to the ANOVA and Tukey test (significance level = 0.05) of the parameters: hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), C-reactive protein (CRP). * p-value referent to the Kruskal-Wallis and Dunn test. Equal letters represent the ones that differ significantly.

Regarding CRP, only 7.76% of children had a characteristic value of infection or inflammatory process, while 92.23% of them had their CRP within normality (<5 mg/L). Table 5 shows that there was no statistically significant association between the presence/absence of subclinical infection and the haematological parameters analyzed.

Table 5. Clinical parameters and their variations according to the presence and absence of subclinical infection

Clinical Parameters	Subclinical infection		p
	Presence (M ± DP)	Absence (M ± DP)	
Hb (g/dL)	10.96 ± 1.226	11.45 ± 1.165	0.261
VCM (fl)	75.60 ± 5.277	75.42 ± 6.376	0.937
HCM (pg)	25.42 ± 1.714	25.26 ± 2.718	0.866
CHCM (g/dL)	33.72 ± 0.748	33.39 ± 1.344	0.487
RDW (%)	12.25 ± 14.085	14.08 ± 3.685	0.466*

Mean (M), Standard Deviation (SD) and p value according to the *Studentt* test (significance level = 0.05) of the parameters: hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), C-reactive protein (CRP). * p-value referent to the Mann-Whitney test.

DISCUSSION

Anemia remains a relevant public health problem in the child population, echoing in the quality of life, especially in regions where life conditions are precarious (Batista-Filho 2008; Leal and Osório, 2010; Borges *et al*. 2009; Castro *et al*. 2011). In this study, it was seen that 25.7% of the children were anemic, result that corroborates other studies (Leal *et al*. 2011; Castro *et al*. 2004; Batista, 2014 unpublished data) carried out in the same region with children from rural areas in the same age group, in which anemia had prevalence rates of 36.6%; 47.5% and 29%, respectively. Anemia happens due to many reasons, so its differential diagnosis is crucial; the red blood cell indices are used to indicate the size, format and morphologic characteristics of red blood cells. They are useful for the diagnosis of iron deficiency after confirmation of anemia, through the determination of hemoglobin concentration (Hadler 2002; Matos 2008). Since the red blood cell indices go through alterations that characterize iron deficiency anemia, the reduced MCV in the presence of anemia favors the diagnosis of iron deficiency anemia. MCH is also modified in iron deficiencies. Below-the-level hemoglobin, together with MCV < 72 fl and/or MCH < 24 pg, suggests iron deficiency (Urrechaga *et al*. 2013; Damodar *et al*. 2013; Hadler 2002; Matos 2008).

Another important parameter for the early diagnosis of iron deficiency anemia is RDW, which reflects the variation in the size of erythrocytes, because, when the iron supply is insufficient, the erythrocytes produced are small and vary greatly in size (anisocytosis), the first manifestation of iron deficiency anemia. This index has an early increase in this situation, indicating lack of iron, even with hemoglobin levels within normality (Urrechaga *et al*. 2013; Damodar *et al*. 2013; Hadler2002; Matos 2008). In the present study, the highest values of RDW and reduced ones in the other red blood cell indices suggest that the anemia present in the studied population is ferropenic. In the study by Pinherio *et al*. 2008 with children from 6 to 59 months from Campina Grande, it was also seen that the red blood cell indices were characteristic of the iron deficiency anemia in the group of anemic children. There was no statistical significance between the sexes of children and the evaluated clinical parameters (Hb, MCV, MCH, MCHC, RDW and CRP). Regarding the age of the children, it was seen that there was statistically significant association among the several age groups and the clinical parameters evaluated, except for MCHC and CRP. It was observed that the levels of hemoglobin increased proportionally to the age group, findings that agree with the ones obtained by Oliveira *et al*. 2014; Oliveira *et al*. 2013; Leal *et al*. 2011.

This can be explained because, from the six month of life on, complementary feeding is introduced, generally rich in dairy foods and cereals that, besides being poor in iron, are rich in phytates, which reduce the bioavailability of this mineral. In addition, the

growth and intense development that characterize this period demand a higher offer of nutrients such as iron (Leite *et al*. 2013; Rawat *et al*. 2014; Woldie *et al*. 2015). The income and the school level of the parents are factors that directly influence the health profile of children, because a higher level implies jobs with higher income and, consequently, better life and health conditions, such as housing, feeding and sanitation services, preventing the appearance of nutritional deficiencies and infections (Kikafunda *et al*. 2009; Tympa-Psirropoulou *et al*. 2008; Oliveira *et al*. 2014). In the current study, the income of most families was around 1 to 2 minimum wages, and the great majority (72.3%) was benefitted by BolsaFamília, a government aid program that complements the family income. Great part of the parents had 5 to 8 years of study. Most children (92.23%) presented CRP values within normality, showing that they did not have any infectious or inflammatory process. In contrast, Knowles *et al*. 2013, when studying children from the rural and urban area in the same age group of this study, saw that 43% of them had CRP>5mg/L, characterizing an infectious or inflammatory process.

Regarding the relationship between the red blood cell indices and the presence of subclinical infection, the results show that there was no significant association, although the red blood cell indices are more characteristic of anemia in children with infection. In studies by Sales *et al*. 2011eKnowles *et al*. 2013 the levels of hemoglobin were also smaller in those children who presented infection, with statistical significance. For the other red blood cell indices, no studies were found in the literature that would cover this relationship. The studies that cover the relation between anemia and subclinical infection are controversial: some point out that the infection alters the metabolism of iron, reducing their concentrations in circulation and, consequently, the synthesis of hemoglobin is harmed, leading to anemia. However, others show that the iron deficiency predisposes the increase of proteins in the acute phase, especially CRP (Rawat 2014; Wieringa *et al*. 2002; Bresnahan *et al*. 2014). More studies that cover the infection and anemia are necessary so that this relation is well clarified and it is another parameter to be used as an aid tool to identify and control anemia. However, it is important to consider that anemia is influenced by socioeconomic, demographic and population health factors, so it is not enough to point out only one cause. In conclusion, in the studied group, anemia figured as a moderate public health problem, although it has presented inferior prevalence than other studies developed in the region. The alterations in red blood cell indices were useful to diagnose anemia as iron deficiency anemia, showing that, although the concentration of hemoglobin is a very useful parameter in the diagnosis of this pathology, it is not enough to its differential classification. Moreover, there was low prevalence of subclinical infection in the studied group, so there was no significant association between the red blood cell indices and this characteristic. The results confirm that iron deficiency anemia remains high in the child population and reinforce the importance of interventions that aim to improve the nutritional state related to this nutrient.

ACKNOWLEDGMENTS

The authors thank the financial support provided by the National Board of Technological and Scientific Development (CNPq) and the coordination of the Higher Education Personnel Training (CAPES) via notice CASADINHO/PROCAD, process 552239/2011-9, as well as the families of the research participants.

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