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Anemia in Children Following an Acute Infectious Illness: Is Systematic Iron Prescription Justified?

Anémie de l'enfant en contexte d'infection aigüe : place de la prescription systématique de fer

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ABSTRACT

Introduction. Although malaria is the most common cause of anemia in children in our context, it is still common practice for health practitioners to prescribe iron to patients with anemia based only on red blood cell indices. The assessment of iron stores is not common practice. **Objective.** To report the prevalence of iron deficiency in acute anemia among children received at the Yaoundé Gyneco-Obstetric and Pediatric Hospital in an infectious context. **Methodology.** This was a cross-sectional study over a period of 6 months, including 1451 Children with infection; aged 6 months to 15 years. Laboratory tests included, full blood count, septic screen depending on the clinical presentation, malaria test, direct stool examination, measurement of iron and ferritin levels in those presenting with biological anemia. The Chi² test was used for comparison and the association between qualitative variables; the threshold of significance was 0.05. **Results.** The sex ratio was 1.27. Children aged 6 to 60 months accounted for 72.9%. Malaria accounted for 68.8% of etiologies. Two-thirds (57.2%) of the patients had biological anemia of which 19.1% were severe. Hypochromic microcytic anemia was more frequent (41.2%) and mostly (83.6%) in children less than 5 years. Serum iron and ferritin levels were measured in 64 patients among whom only 14 of them had low serum iron levels and 2 with low serum ferritin levels. **Conclusion.** The prevalence of anemia in children received for infectious problems was high but almost all the children had normal or high iron.

RÉSUMÉ

Introduction. Le paludisme est la première cause d'anémie chez l'enfant camerounais. La prescription de fer au cours d'anémies en contexte infectieux est basée sur les indices érythrocytaires. L'évaluation des réserves en fer n'est pas courante. **Objectif.** Déterminer la prévalence de la carence en fer au cours des anémies aiguës en contexte infectieux chez l'enfant reçu à HGOPY. **Méthodologie.** Il s'agissait d'une étude prospective transversale analytique portant sur 1451 enfants âgés de 6 mois à 15 ans. Après examen clinique nous avons réalisé une Numération Formule Sanguine, un bilan infectieux selon l'orientation, un dépistage du paludisme, et l'examen direct des selles. Le fer sérique et la férritinémie ont été mesurés chez les patients présentant une anémie biologique. Le test Chi² a été utilisé pour la comparaison et l'association entre les variables qualitatives. Le seuil de significativité était de 0,05. **Résultats.** Le sex-ratio était de 1,27 et 1058 (72,9%) enfants compris entre 6 et 60 mois. Deux tiers (57,2%) des enfants avaient une anémie biologique et 11% étaient sévères. Les anémies microcytaires hypochromes étaient plus fréquentes (41,2%), à majorité chez les moins de 2 ans (76,2%). Le paludisme représentait 2/3 (68,8%) des étiologies. Les taux sériques de fer et de ferritine mesurés chez 64 patients révélaient une hyposidérémie chez 14 (21,9%) et seulement 2 (3,1%) avaient une hypoférritinémie. **Conclusion**. L'anémie est fréquente chez les enfants en contexte infectieux. Cependant, leurs réserves de fer sont pour la majorité normales ou élevées. La supplémentation systématique dans ces cas n'est pas justifiée.

INTRODUCTION

Anemia is common in children and affects more than 3.5 billion people in developing countries. It is defined as a hemoglobin level that is two standard deviations below the mean for age (1–3) . In Cameroon, two out of three children aged between 6 and 59 months are affected (4). Severe anemia is the first cause of death in the emergency unit of the Mother and Child Center of the Chantal Biya Foundation in Yaoundé (5). The causes of anemia vary with age. Iron deficiency is thought to be the most common cause of anemia globally (1). Meanwhile, other nutritional deficiencies, acute and chronic inflammation, parasitic infections, and inherited or acquired disorders that affect hemoglobin synthesis, red blood cell production or red blood cell survival, can all cause anemia (1). Malaria is the leading cause of anemia in children before other infections in Cameroon, accounting for almost 40% of the annual household expenditure (5–8). Although malaria is the most common cause of anemia in children in our context, it is still common practice for health practitioners to prescribe iron to patients with anemia based only on red blood cell indices (Mean Corpuscular Volume (MCV) and Mean Corpuscular Hemoglobin Concentration (MCHC)). The assessment of iron stores is not common practice. We carried out this prospective cross sectional study in order to determine the prevalence of iron deficiency in acute anemia among children received at the Yaoundé Gyneco-Obstetric and Pediatric Hospital in an infectious context with the hypothesis that anemia following an infectious event is not necessarily associated with iron deficiency.

MATERIALS AND METHODS

We carried out a prospective cross-sectional study for a period of 7 months from June 1st to December 31st, 2010 at the pediatric service of the Yaoundé Gyneco-Obstetric and Pediatric Hospital (YGOPH).

The population was made up of children aged 6 months to 15 years presenting with fever and/or infectious event; whose parents accepted to enter the study. Excluded from the study were patients with known sickle cell anemia or discovered during the study period, cancer and any child on iron supplementation.

Procedure

The clinical evaluation started with an interrogation during which we noted the age and sex, main complaint and past medical history. Then a thorough physical examination of each patient was done. Laboratory investigations were requested based on the clinical diagnosis. These included: complete blood count, thick/thin blood smear for malaria parasite, blood cultures, urine cultures, analysis of cerebrospinal fluid and culture, direct stool examination and chest x-rays. Haemoglobin electrophoresis was performed if the parents did not know it.

The red blood cell indices [Haemoglobin (Hb) level, Mean Corpuscular Volume (MCV) and Mean Corpuscular Haemoglobin Concentration (MCHC)] were noted. Those with biological anemia under went more investigations to determine the iron stores. These included the measurement of serum iron and ferritin levels at "*Centre Pasteur du Cameroun* (CPC) Yaoundé. For children who received a blood transfusion, the samples were taken 48 to 72 hours after the blood transfusion concomitantly with the control complete blood count.

Biological analyses

They were performed on a 5 mL sample of peripheral venous blood. The complete blood counts were performed at the YGOPH by the automaton Hospitex Diagnostic Hema Screen® 18. The measurement of serum ferritin and iron levels was performed with immunometric chemiluminescence using the 1000 & 2000 Siemens® immune system. The other work-ups were carried out at the bacteriology and parasitology laboratories while X-rays were done at the medical imaging department of the YGOPH.

Operational terms

We subdivided the sample into three age groups: 6-60 months, 61-120 months, 121-180 months.

According to the WHO, anemia is defined in children for a haemoglobin level below 11 g/dL (1); we defined four levels of haemoglobin: no anemia for Hb> 11g/dL, mild anemia for Hb between 10.0 and 10.99 g/dL, moderate anemia for Hb between 7.0 and 9.99 g/dL and severe anemia for Hb <7 g/dL (1). The MCHC was considered normal when it was greater than 25 pg, below 25 pg there was hypochromia (1,9) .

Age-specific normal MCV standards were 70-86 fL between 6 and 24 months, 73-89 fL between 24 and 60 months, 74 and 91 fL between 60 and 180 months (2,10); the normal MCV corresponded to normocytosis, a high and low MCV corresponded to macrocytosis and microcytosis respectively. We used CPC reference values of 0.5 to 1.5 mg/L for serum iron levels and 9 to 120 ng/L for serum ferritin levels.

Statistical analysis

The statistical analysis was done using the Epi info 3.5.1 software. Quantitative variables were expressed in terms of mean, while qualitative variables were in proportions. The Chi^2 test was used for comparison and association between qualitative variables; the Anova test was used to compare the means between more than 2 groups of numerical variables; the threshold of significance was 0.05.

RESULTS

A total of 1451 children were recruited, of whom 813 (56.0%) were boys and 638 (44.0%) were girls; giving a sex ratio of 1.27 (Table 1). Children between 6 and 60 months were the most represented (72.9%). There was no significant difference between sexes in the different age groups (p = 0.23).

Table 1: Characteristics of children and haemoglobin level with regards to the age group.

Age (months)	Mean HB (g/dL)	Boys; N (%)	Girls; N (%)	Total (%)
6-60	9.96 ± 2.31	604 (41.6)	454 (31.3)	1058 (72.9)
61-120	10.4 ±2.58	150 (10.3)	123 (8.5)	273 (18.8)
121-180	11.18 ± 2.35	59 (4.0)	61 (4.2)	120 (8.3)
Total		813 (56.0)	638 (44)	1451 (100)
p-value		0.03		

Biological anemia was found in 830 children, giving a prevalence of 57.2%. 614 children (74.0%) with anemia were aged 6 to 60 months (Table 2). Hypochromic microcytic anemia - 342 (41.2%) patients, and normochromic normocytic anemia - 295 (35.5%) patients were the two most common types of anemia (Table 2).

Table 2: Classification of anemia according to MCV and MCHC.

Type of anemia	Total (%)	Age group (months) N (%)	
		6 - 60	> 60
Microcytic Hypochromic	342 (41.2)	286 (83.6)	56 (16.4)
Normocytic Normochromic	295 (35.5)	195 (66.9)	100 (33.1)
Microcytic Normochromic	96 (11.6)	57 (59.4)	39 (40.6)
Normocytic Hypochromic	63 (7.6)	54 (85.7)	09 (14.3)
Macrocytic Normochromic	31 (3.7)	19 (61.3)	12 (38.7)
Macrocytic Hypochromic	3 (0.4)	3 (100)	00 (00)
Total	830 (100)	614 (74)	216 (26)

Anemia was mild to moderate in 80.6% of patients, normocytic (45.0%) or microcytic (49.0%), and normochromic in 51% of patients (Table 3). In children aged 6 to 60 months, the anemia was more compared to children aged 61 to 120 months (p = 0.03). Meanwhile there was no anemia in children above 120 months (Table 1).

Table 3: Classification of anemia based on haemoglobin level.

Hemoglobin level	Class	Number of patients N (%)
10.0 - 10.99 g/dL,	Mild	297 (35.8)
7.0 - 9.99 g/dL	Moderate	374 (45)
<7 g/dL.	Severe	159 (19.2)
Total		830 (100)

Malaria accounted for more than 2/3 of infectious aetiologies with 68.8% (Table 4). Among children diagnosed for malaria, 108 (18.8%) had severe anemia and received blood transfusion. Only 314 (37.5%) used insecticide-treated mosquito bed nets and 233 (28.1%) were dewormed within the 3 previous months. All the children had good nutritional status for age.

Table 4: Infectious aetiologies associated to anemia.

Pathologies	Counts (n=830)
***Plasmodium falciparum* malaria**	571 (68.8)
Bronchopneumonia	54 (6.5)
***Shigella sp/others bateria* enteritis**	30 (3.6)
Super infection of bronchitis	25 (3.0)
Meningitis	20 (2.4)
Pleuropneumonia	27(3.3)
Tonsilitis	30 (3.6)
Severe sepsis with pulmonary focus	40 (4.8)
Urinary tract infection.	33 (4.0)

Serum iron and ferritin levels were measured in only 64 (7.7%) patients with anemia. Amongst these children, the mean serum iron level was 1.11 ± 1.1 mg/L and mean serum ferritin level was 583 ± 892.8 ng / L. Only 40.6% of these children had microcytic hypochromic anemia. High serum iron levels were noticed in 69.2%, while almost all of them (96.8%) had normal or high serum ferritin levels. Only 2 (3.1%) patients had low serum ferritin levels on hypochromic microcytic anemia (Table 5). There was no significant association between the classes of anemia based on the MCV, MCHC, serum ferritin and iron levels (p = 0.072).

Table 5: Distribution of anemia in according to MCV, MCHC, serum iron and ferritin levels.

Type of anemia	Ferritin level N (%)		Iron level N (%)		Total N (%)
	Normal/ high	Low	Normal / high	Low	
Microcytic hypochromic	24 (92.4)	2 (7.7)	18 (69.2)	8 (30.8)	26 (40.6)
Microcytic Normochromic	16 (100)	0 (0)	12 (75)	4 (25)	16 (25)
Normocytic Normochromic	12 (100)	0 (0)	12 (83.3)	0 (0)	12 (18.8)
Normocytic Hypochromic	8 (100)	0 (0)	8 (100)	0 (0)	8 (12.5)
Macrocytic Normochromic	2 (100)	0 (0)	2 (100)	0 (0)	2 (3.1)
Total	62 (96.8)	2 (3.1)	52 (78.1)	12 (21.9)	64 (100)

DISCUSSION

We carried out this study with the hypothesis that anemia following an infectious event is not necessarily associated with iron deficiency despite evidence from the red blood cell indices.

Because of financial constraints, the iron status could only be measured in a few patients in the present study and in all the patients, the infectious work up needed to confirm diagnosis was not complete. These could have introduced some bias in the study. Meanwhile, the small number (64) patients in whom iron stores were measured showed the real picture of iron status in anemic children in the context of infection.

We included only infants aged 6 months and over because iron reserves at birth and iron supplied by breast milk covers children's needs during the first six months of life (10). The various paediatric age groups were included to bring out the most vulnerable groups. The under 60 months age group made up about 73% of all the children with anemia, similar to the results described by WHO (10). There was no statistically significant difference between the two sexes, findings close to those of other authors (13,14) .

The prevalence of anemia in our study was 57.2%; lower than the 68% reported in Cameroon in the 2011(4); but higher than the 42.8% reported in 2008 in the same context (13). The difference could be attributed to the difference in study population since the sample of the last study included only the 60 to 120 months age group, which is known to be less susceptible to anemia (13,14). Severe anemia was found in 11% of children consistent with the findings of other authors in Cameroon (5,6) .

Normochromic anemia was more frequent than hypochromic anemia correlating with the finding of Abissey et al (14). Microcytic and normocytic anemia were evenly distributed, contrary to the results obtained by other researchers, who found that microcytic anemia was two times more frequent than normocytic anemia (14,15). This difference may be due to age-specific MCV standards that differed in our series. Macrocytic anemia, on the other hand, was not frequent. This result is similar to those reported by Abissey et al and Atanda et al (14,15). Macrocytosis is rare in the normal pediatric population although very common in sickle cell patients, who were excluded from our study.

Hypochromic microcytic anemia was the most frequent type of anemia followed by normochromic normocytic anemia. This result differs from those found earlier in Cameroon, Ivory Coast and Congo (13–15) . This may be so because, our population was predominantly under 5 years of age, with the proportion of less than 24 months representing the vast majority of patients with microcytic anemia, thus opening discussion on the possibility of iron deficiency generated during the food diversification phase. Younger children were significantly more anaemic than older children. This could also reflect the increased iron needs in younger children with increased growth velocity (3,9,16) .

Previous studies in Cameroon revealed that malaria was a cofactor in more than 70% of children with anemia (5,6,13) correlating with the 68.8% in our series. Malaria is also a factor in the severity of anemia in children; in our series, similar to reports by Forlack et al (18), and Tchokoteu et al in Yaoundé (19). The common practice is for children to be put on iron blood tonics after transfusion despite the fact that anemia from malaria is caused by hemolysis and not iron deficiency. On the other hand, intestinal parasites are also implicated in the occurrence of childhood anemia (20). We could not establish a direct link between intestinal parasites and the occurrence of anemia. However, helminthiasis is strongly associated with the occurrence of childhood anemia (13,15,21).

The red cell indices are often used to characterise iron deficiency anemia (22). Serum iron level alone is not sufficient and is not indicated for the diagnosis of iron deficiency anemia or iron overload in acute inflammation because it can be low independently of the iron reserves (23,24). The measurement of serum ferritin level has been shown to be the parameter of choice for initial diagnosis of iron deficiency and overload, although bone marrow study is the gold standard (22–24). Our results showed that 78.1% of the patients had serum iron levels in the normal range or higher. This result is in contrast to the findings of Bergeret et al in Yaoundé in the 1960s (25) who found that African child before the age of 3years had very low iron levels compared to European child. This difference could be explained by the fact that they excluded children with malaria and the high incidence of malnutrition in their sample. In our study, all the children had normal nutritional status. Only 3% of children who benefited from the serum iron investigations had low ferritin and serum iron levels, concomitantly with microcytic hypochromic

anemia reflecting true iron deficiency. This correlates with the results of the European Growth Study (16).

Iron supplementation prevents and improves the health status in deficient children; however, bringing iron as an oral supplement to the non-deficient child may increase the incidence and possibly the severity of malaria as well as other infections (26,27).

In light of our findings, iron deficiency anemia in association with an infectious episode cannot be diagnosed based on the red cell indices alone. Studies to evaluate iron stores in such patients will help determine true iron deficiency. Therefore, the prescription of iron in a child with anemia following an infectious episode should be judicious. This should be done only after the infection has been treated and the proof of iron deficiency made.

CONCLUSION

The prevalence of anemia in infants received at the YGOPH for infectious diseases is high but is not always due to iron deficiency. Systematic iron supplementation without knowledge of serum ferritin and iron levels is therefore not justified.

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CONTRIBUTION OF AUTHORS:

Mah Evelyn designed the study, varied data and wrote the manuscript; Nguefack Félicitée and Mbassi Awa read the manuscript; Nkeck Jan Rene edited the manuscript; Mouto Ruth collected and analysed the data; Chiabi Andreas edited the manuscript; Nguefack Seraphin verified the data; Obama Marie Therese supervised the work.

CONFLICT OF INTEREST

The authors state that there is no conflict of interest.

ETHICAL CONSIDERATIONS

We obtained an authorization from the HGOPY research commission for the realization of this study and the recruitment of our patients in the paediatric department of the hospital. Informed consent was obtained verbally from the parents of the children included in the study. The results of the various examinations were given and explained to the parents.

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