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PREVALENCE OF AND RISK FACTORS FOR ANEMIA IN YOUNG CHILDREN IN SOUTHERN CAMEROON

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Abstract. Anemia during childhood remains a major public health challenge in sub-Saharan Africa. To determine the prevalence of and the main risk factors for anemia in young children, we conducted a longitudinal survey in Ebolowa in southern Cameroon. Children were enrolled in two cohorts and followed during a three-year period: the first cohort was composed of 122 children from 0 to 36 months of age and the second cohort was composed of 84 children from 24 to 60 months of age. The two cohorts were followed weekly for symptomatic malaria, monthly for both symptomatic and asymptomatic malaria, and every six months for hematologic data; the children were grouped into six-month age groups. The prevalence of anemia (hemoglobin [Hb] level < 11 g/dl) was the highest in the six-month-old age group (47%) and the age-related evolution clearly showed a decrease in the prevalence from three years of age. Thus, 42% of the children less than three years of age were anemic, while 21% of the children between three and five years of age were anemic. The lowest mean $\pm$ SD Hb content (10.7 ± 2.1 g/dl) was observed in the six-month-old children and a regular improvement in the Hb level occurred from six months to three years of age. A stabilization was observed at a level of approximately 12 g/dl. At any age, there was no difference in mean Hb levels between children with AS and AA Hb genotypes. Hookworm infection was diagnosed in two children in the study population. Results of a multivariate analysis showed that placental malaria infection was the strongest risk factor for anemia in the six-month-old children (odds ratio [OR] = 3.6; 95% confidence interval [CI] = 1.1–12.3) and was independent of the frequency of parasitemia, parasitemia at the time of Hb measurement, or microcytosis. In the one-year-old age group, microcytosis was a significant factor related to anemia (OR = 2.8, 95% CI = 1–7.8) pointing out the role of iron deficiency at this age. Parasitemia at the time of Hb measurement was significantly associated with anemia in all age groups (except in 54- and 60-month-old groups). Strategies to decrease the prevalence of anemia in young children in southern Cameroon should include chemoprophylaxis for pregnant women, prevention of acquired malaria infection in both pregnancy and infancy, and prevention of nutritional iron deficiency.

Anemia impairs normal development in children and it constitutes a major public health problem in young children in the developing world with wide social and economic implications. Thus, decreased physical exercise tolerance and intellectual performance have been associated with mild anemia, which may lead to a slowdown of growth in children.[1, 2] In sub-Saharan Africa in children less than five years of age, the prevalence of anemia varies from 43% in Zaire to 74% in Tanzania.[3, 4] Its etiology in tropical countries is multifactorial: thus, the most important risk factors need to be identified for prevention strategy. Anemia is commonly associated with nutritional deficiencies such as iron deficiency, the main factor responsible for microcytic anemia, while folate or vitamin B_{12} deficiencies are responsible for macrocytic anemia.[1, 5] Similarly, parasitic diseases such as malaria and ankylostomiasis have been reported to lead to a high prevalence of anemia during childhood.[3–6] Sickle cell disease has been also recognized as an important risk factor for anemia in sub-Saharan countries.[5, 7] However, the relative contributions of these etiologies remain unclear. We conducted a prospective study in southern Cameroon to analyze the epidemiology of anemia and to specify the role of malaria, compared with others risk factors, in the development of anemia in 206 children less than five years of age.

SUBJECTS AND METHODS

Study site and survey method. The study was carried out between January 1993 and December 1995 in Ebolowa, a city of approximately 35,000 inhabitants. Ebolowa is located in southern Cameroon, 160 km south of Yaounde, the capital city. Malaria is mesoendemic and transmission is perennial with sporozoite inoculation rates of approximately 62 infective bites per person reported annually (Le Goff G, Toto JC, unpublished data).

Children were enrolled in the two hospital-maternity units in Ebolowa after informed consent was obtained from their parents. Two cohorts were defined and followed for 30 months (for the last enrolled) to 36 months (for the first enrolled). At birth, children were included in cohort I and their older sister or brother, if any, were included in cohort II. In the latter cohort, children less than 24 months of age or more than 36 months of age were excluded. At enrollment, socioeconomic and demographic information was obtained. In addition, in cohort I the newborn was weighed and a placental specimen was collected to assess placental malaria infection. No hematologic measurements were available at delivery either for the newborn or the mother. Subsequently, follow-up was the same in the two cohorts and comprised weekly, monthly, and half-yearly surveillance.

Weekly. Every week, a home visitor asked for the child's history of fever and the axillary temperature was measured. A thick blood smear for malaria parasite examination was collected in a case with fever (temperature ≥ 37.5°C). Febrile children who were found to be parasitemic were treated with amodiaquine or chloroquine, 25 mg/kg over a three-day period, or were referred to the hospital in case of severe symptoms.

TABLE 1
Distribution of the children by age group at the time of hemoglobin measurement

Age group (months)	Mean age (SEM) (months)	Cohort I	Cohort II
6	6.5 (0.07)	95	0
12	11.9 (0.07)	107	0
18	17.9 (0.11)	99	0
24	23.9 (0.07)	90	20
30	29.7 (0.1)	85	41
36	35.5 (0.15)	21	65
42	41.1 (0.18)	0	65
48	47 (0.17)	0	65
54	53.7 (0.26)	0	41
60	60.7 (0.4)	0	47

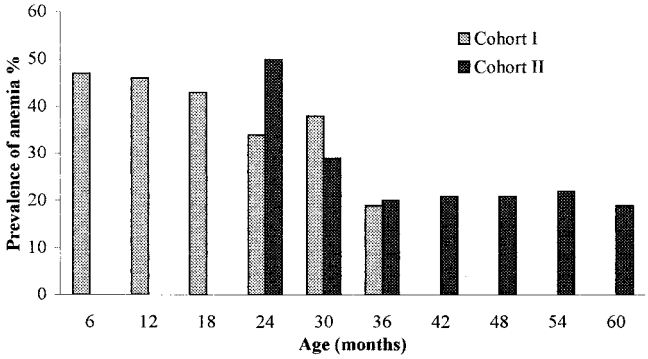

FIGURE 1. Prevalence of anemia by age group and cohort.

Monthly. Every month, a thick blood smear for malaria parasite examination was collected systematically, even from asymptomatic children.

Six months. A blood specimen was obtained every six months for the hematologic data and once for hemoglobin (Hb) genotype assessment.

After 24 months of follow-up, a stool specimen was collected for microscopic parasitic examination. The protocol was approved by the Ethic and Scientific Committees of the Cameroon Ministry of Public Health.

Laboratory methods. Hematologic measurements were carried using automated methods with a Coulter® counter (Coulter Electronics, Hialeah, FL) that measured the Hb and the mean corpuscular volume (MCV), calculated the hematocrit, and counted the number of red and white blood cells. Anemia was defined as an Hb level < 11 g/dl and severe anemia as an Hb level < 7.1 g/dl.[1, 8–11] For children less than three years of age a normal MCV ranged from 70 fl to 86 fl and for older children a normal MCV ranged from 73 fl to 89 fl.[1]

Thick blood smears and placental appositions were stained with Giemsa. Parasite densities (parasites/μl) in thick blood smears were calculated from the number of parasites per 200 white blood cells corrected for 8,000 white blood cells/μl. *Plasmodium falciparum* was the major species (97%) encountered; thus, parasitemia was defined as the presence of *P. falciparum* asexual stages in the blood films. Placental smears were evaluated only for the presence or absence of parasites.

Hemoglobin genotypes was determined by Hb electrophoresis on cellulose acetate gels with alkaline buffer. Parasitic stool examinations were performed using Kato's method.[12]

Statistical methods. Statistical analysis was performed using Epi-Info 5.0 (Centers for Disease Control and Prevention, Atlanta, GA) and EGRET (Serc, Seattle. WA) computer software programs. Chi-square or Fisher's exact tests were used for contingency table data, means were compared with Student's *t*- or Kruskal-Wallis tests, and Spearmann's test was used for determining the correlation coefficient. Multivariate analysis was done using a logistic regression model adjusting for the possible confounding variables that were significant in the univariate analysis. A *P* value less than 0.05 was considered statistically significant.

The analysis of anemia was made through subsequent surveys every six months from the ages of six months and 24 months in cohort I and cohort II, respectively. The children were grouped together in six-months age groups because of the periodicity of the hematologic data. Each age group was composed of children of the same age ($\pm$ 2 months). All blood smear results from the half-year period preceding the Hb measurement were taken into account for the analysis of the relationship between anemia and malaria.

RESULTS

Two hundred six children were enrolled in the study. One hundred seventy-two children enrolled at birth in cohort I were followed to the age of 30 or 36 months, and 84 children enrolled at 24 or 36 months in cohort II were followed to the age of 60 months. Table 1 shows the distribution of the study population. An average of 60% of the children were seen at the weekly and monthly visits. A blood sample was not collected from all children every half-year period because some children were absent. In cohort I, the end of the follow-up occurred at 36 months of age for the first children enrolled and at 30 months for the last enrolled, and in cohort II, children were included from 24 to 36 months of age. Thus, the size of the age groups was variable. Nine children died during the study period: seven in cohort I and two in cohort II. Since death occurred almost always outside a health center, causes of death were not clearly established. From verbal review, two children were likely to have died of severe anemia related to malaria. The others, who died in the hospital, probably died of various causes such as pneumonosis, hepatitis, or accidental death, but not from malaria.

The evolution of the prevalence rates of anemia with age is shown in Figure 1. At a given age for the 24-, 30-, and the 36-month age groups, which comprised children of the two cohorts, there were no significant differences in the prevalence of anemia between the two cohorts. Moreover, the age-related evolution of this prevalence was similar in the two cohorts, with a similar decrease after 30 months of age. Figure 2 shows the mean Hb content by age group. There were no significant differences in the mean Hb content between the two cohorts at a given age and the prevalence of malaria, and the age-related evolution was similar in the two cohorts. Therefore, the two cohorts were analyzed together. Mean Hb levels were similar for boys and girls. The children in the six-month age group had the lowest mean Hb content (10.7 g/dl) and the highest prevalence of anemia (47%). Similarly, this age group had more severe anemia (n

FIGURE 2. Mean ± SEM hemoglobin (Hb) levels by age group and cohort.

TABLE 2
Correlation between the frequency of malaria episodes (Ra) and Hemoglobin level

Age group (months)	Correlation coefficient and (95% confidence interval)	Mean Ra	n	*P*
6	−0.35 (−0.54; −0.11)	0.14	65	0.0025
12	−0.18 (−0.38; 0.04)	0.16	83	0.1
18	−0.24 (−0.44; −0.02)	0.22	78	0.025
24	−0.42 (−0.59; −0.22)	0.29	80	<0.0005
30	−0.26 (−0.45; −0.05)	0.36	85	0.01
36	−0.31 (−0.53; −0.06)	0.39	58	0.01
42	0.11 (−0.17; 0.38)	0.39	51	0.25
48	−0.30 (−0.52; −0.04)	0.39	56	0.025
54	−0.38 (−0.63; −0.06)	0.39	37	0.01
60	−0.03 (−0.35; 0.29)	0.37	37	0.5

* Ra = rate of the number of thick blood films that revealed malaria parasites and the number of thick blood films collected per child.

= 5) than the others (n = 3). Thereafter, the mean Hb content increased until 36 months and then stabilized at approximately 12 g/dl. The prevalence of anemia decreased from 47% in the six-month-old children to 21% in children greater than 30 months of age.

The prevalence of microcytosis was highest in the 12-month age group (56%) and it then decreased and stabilized at a value of approximately 20% after 18 months. Macrocytosis was not common in the study population and the number of macrocytic children did not exceed five in each age group.

Two children were homozygous for the sickle cell gene (SS). They were severely anemic at the age of 18 months and received blood transfusions. Twenty-six percent (53 of 204) of the children were heterozygous for the sickle cell gene (AS) and their Hb levels did not differ from those of children with the normal Hb genotype (AA) for any age group. The prevalence of ankylostomiasis was very low in the study population; only two of 201 children had hookworm eggs in their stool.

Thirteen percent of the thick blood smears showed *P. falciparum* in the six-month age group. This rate increased regularly with age until three years of age and then stabilized at approximately 40%. Ninety-two percent of the thick blood smears were collected in children without febrile illness. To assess the frequency of parasitemic episodes experienced in the preceding half-year period and to adjust for the number of thick blood films collected per child, we used the percentage of thick blood films that revealed malaria parasites. Children for whom we collected less than three thick blood smears during the six-month period were excluded from this assessment (25% of the children in the six months age group, and less than 15% in the older ones were excluded). The mean rate ranged from 14.3% in the six-month -old children to 38.6% in those greater than three years of age (Table 2). There were significant negative correlations in all age groups (except in the 42 and 60 months age groups) between the rate and the Hb level (Table 2). The mean rate in anemic children increased from 24% in the six months age group to 40% in the 24 months age group and varied between 40% and 60% until 60 months of age. In nonanemic children, it increased from 6% in the six months age group to 22% in the 24 months age group and varied between 26% and 38% until 60 months of age. In addition, anemia was significantly associated with the presence of parasites in the blood at the time of sampling in all age groups. The children found to be parasitemic concurrently to the sampling for Hb measurement were 4–7 times more likely to be anemic. However, children found to be parasitemic at the time of hematologic data were also more frequently infected with *P. falciparum* in the preceding half-year period in every age group.

Placental malaria infection was diagnosed in 23% of the placental appositions. Eighty-six in the six months age group had placental appositions at birth, and 77 of these 86 had an Hb measurement at six months of age. The univariate analysis showed a strong association between anemia for the six-month-old children and placental malaria infection. In this age group, a history of placental malaria infection was observed in 41% of the anemic children and in only 14% of the nonanemic children ($P = 0.007$, OR = 4.3, 95% CI = 1.3–15.3). This association did not persist after six months of age. However, the frequency of parasitemia between birth and the age of six months had a tendency to be higher when the placenta was infected by *P. falciparum* (rate = 24.5% versus 12.3% with and without placental malaria infection, respectively; $P = 0.06$). This observation could explain the increased risk of anemia in children born of a placentally infected mother; thus, the frequency of malarial episodes may act as a confounding variable for the relationship between anemia and placental malaria infection.

We performed a multivariate analysis through a forward logistic regression model. This model included qualitative variables that were concurrent parasitemia to Hb measurement, placental malaria infection, and microcytosis, while the frequency of parasitemia was included as a quantitative variable. Results for the six-, 12-, and 18-month age groups are shown in Table 3. In the six-month-old children, placental malaria infection remained associated with anemia independently of the frequency of parasitemic episodes or concurrent parasitemia. In the one-year-old age group, microcytosis was a significant factor related to anemia, suggesting the role of iron deficiency in the one-year-old children. Parasitemia at the time of Hb measurement was significantly associated with anemia in all age groups (except in the 54- and 60-month groups). In the six-month age group, the adjusted OR for this factor was close to significance ($P = 0.06$). It was the only factor that remained associated with

TABLE 3
Risk factors for anemia in the six-month-, 12-month- and 18-month-old children; multivariate model*

Risk factor	Adjusted odds ratio (95% CI)	*P*
Six-month age group (n = 77)		
Frequency of parasitemia (Ra)	7.4 (0.4–123)	0.16
Concurrent parasitemia to Hb measurement	4.3 (0.9–19)	0.06
Placental malaria infection	3.6 (1.1–12.3)	0.04
Microcytosis	0.8 (0.3–2.6)	0.7
12-month age group (n = 86)		
Frequency of parasitemia (Ra)	2.3 (0.4–14.5)	0.4
Concurrent parasitemia to Hb measurement	8 (2.2–29)	0.002
Placental malaria infection	1.1 (0.4–3.6)	0.8
Microcytosis	2.8 (1–7.8)	0.05
18-month age group (n = 81)		
Frequency of parasitemia (Ra)	1.5 (0.25–8.6)	0.7
Concurrent parasitemia to Hb measurement	4.5 (1.4–14.7)	0.012
Placental malaria infection	0.7 (0.2–2.3)	0.5
Microcytosis	1.2 (0.4–3.1)	0.7

* CI = confidence interval; Ra = rate of the number of thick blood films that revealed malaria parasites and the number of thick blood films collected per child.

anemia after one year of age, and the results of the multivariate analysis were similar to those observed in the 18-month age group.

DISCUSSION

The present study confirms the high prevalence of anemia previously observed in children in central Africa. In Cameroon north of Yaounde, Rikong and others reported a prevalence rate of 37% in children less than four years of age (unpublished data). Forty-three percent of the children less than five years of age who were brought to the emergency ward of a hospital in Kinshasa, Zaire were anemic.[3] Moreover, in a three-year longitudinal survey with a half-year follow-up, our results specified the age-related decrease in the prevalence of anemia in children from six to 60 months of age. Our study clearly showed a decrease in the prevalence of anemia after 30 months of age (42% versus 21% before and after 30 months of age, respectively; $P < 10^{-8}$).

The highest prevalence rate of anemia (47%) occurred in the six-month-old children. In this age group, anemia was associated with placental malaria infection and this association remained significant after controlling for other factors such as frequency of parasitemic episodes encountered during the preceding six-month period, parasitemia at the sampling time for Hb measurement, and microcytosis. Placental malaria has often been associated with low birth weight.[13–15] In the present study, there was no significant difference in birth weight between the children born of a placentally infected mother and those born of mothers with parasite-free placentas. In a recent study conducted in Malawi in infants less than four months old, Redd and others suggested that placental malaria infection may interfere with the hematologic status of the infant independently of birth weight and prematurity.[16] Our results are in agreement with this hypothesis of a direct relationship between placental malaria infection and anemia of the infant. In addition, our data show that this relationship may persist until six months of age. Few studies have analyzed the possible mechanism of the anemia in the infant induced by the placental infection by *P. falciparum.* Physical alterations of the trophoblastic membrane may decrease nutritional exchanges, such as iron, folate, and vitamin B_{12}, between the mother and her fetus.[17] Alternatively, immunologic mechanisms responsible for hemolysis or dyserythropoiesis have been suggested.[16]

In older children from one to four years of age, parasitemia at the time of sampling for Hb measurement was the only (except for the 12-month-old children) factor that remain associated with anemia independently of the frequency of parasitemic episodes, placental malaria infection, and microcytosis that probably reflects iron deficiency. This result shows that *P. falciparum* infection is strongly associated with hemolytic anemia in young children in malaria-endemic areas. Several previous studies have demonstrated an association between anemia and symptomatic malaria.[3, 4] Since most of the children in our study were asymptomatic, we suggest that asymptomatic malaria is also a strong risk factor for anemia in children.[16, 18–22] The frequency of parasitemia was not a significant risk factor in the multivariate model, suggesting that the mechanism responsible for malaria-related anemia involved predominantly acute hemolysis as compared with dyserythropoiesis or ineffective erythropoiesis due to recurrent parasitemia.[19, 20, 23, 24]

The role of the parasite density is still unclear. In our study among parasitemic children, the Hb level was not related to parasite density. While some investigators found a significant negative correlation between Hb level and parasite density,[25] others, including our group, failed in finding such a correlation, although they identified malaria as a risk factor for anemia.[3, 4, 25]

The prevalence of microcytosis may reflect the prevalence of iron deficiency.[1] However, assessment of iron deficiency only by microcytosis without serum iron and ferritin measurements is not specific enough and microcytosis in this area might be partly explained by alpha-thalassemia minor.[1] In our study, the prevalence of microcytosis was high until two years of age and 50% of the younger anemic children were microcytotic. High prevalences of iron deficiency–related anemia in children have been described in Tanzania (40%) and Nigeria (41%).[4, 26] In a study conducted in Nigeria, iron deficiency was found to be responsible for 57%

of the anemia in 1–15-year-old children.[7] In the current study, multivariate analysis showed an association between microcytosis and anemia in the 12-month age group. This result is not surprising since iron deficiency is common in African children in the second year of life, and this has been related to prolonged breast-feeding.[1, 4] In the study population, weaning occurred at approximately 18 months of age. The low iron content of breast milk, the lack of other iron-rich food, and the age-related increase in iron requirements predispose children to the depletion of iron stores that occurs at approximately one year of age. In addition, the major components of the diet in young children in developing countries are cereals and roots, which are not favorable for iron absorption as compared with meat or fish.[1, 5] After two years of age, anemia and microcytosis decrease, and dietary and iron requirement changes may be partly responsible for this improvement.

Since anemia occurs in 45% of the children less than two years of age in south Cameroon, it remains a major public health problem. Strategies to decrease the prevalence of anemia in young children need to be developed in this area. In the present study, both placental malaria and parasitemic episodes that occurred in the children were associated with anemia in infants. Thus, chemoprophylaxis of pregnant women and prevention of acquired malaria infection by the use of bed nets will likely reduce the prevalence of anemia in young children. To improve the nutritional status of the children and to prevent the iron deficiency–related anemia, iron-rich food supplements are required in addition to breast-feeding early in infancy, as well as iron supplementation in children less than two years of age.

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