ORIGINAL ARTICLE

Emergence of Severe Malaria in Children Over 5 Years in Libreville

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ABSTRACT

Introduction and Background: Prevention measures against malaria in pregnancy and children under 5 years in Gabon have led to a reduction of morbidity and mortality of young children. We aimed to estimate the prevalence of severe malaria and to determine epidemiological profile of severe malaria in children in Libreville. **Materials and Methods:** We conducted a prospective study in pediatric wards of three public hospitals in Libreville. We included any child aged 0–15 years, hospitalized for the proven malarial episode: Thick drop smear positive and/or positive rapid diagnostic test. The severity of malarial access was asserted using the World Health Organization malaria severity criteria 2011. **Results:** Of the 2655 hospitalized children during this period, 596 (22.9%) were for proven malarial access, of which 206 (7.9%) had at least one severity criterion. The mean age of children with severe malaria was 56.1 ± 40.9 months; the sex ratio was 1.1. Among cases with severe malaria, those aged <60 months were 63.1% (*n* = 130/206), those over 60 months were 36.9% (*n* = 76/206). The cerebral forms were more important in the over 5 years: 55.3% odds ratio (OR) = 3, 9 (confidence interval [CI] 95% [2–8.3]). Anemic forms were most common in those younger than 5 years of age 66.9% OR = 4.13 (CI 95% [2.2–7.90]). **Conclusion:** Improved antimalarial protection for children under 5 years has led to an epidemiological transition, resulting in an increased prevalence of severe access among children over 5 years. It seems appropriate to explore preventive measures for this age group.

Key words: Child, epidemiological transition, severe malaria

INTRODUCTION

Malaria is a global public health problem whose importance has motivated its inclusion in the 6th millennium development goal, namely, to reduce the number of malaria cases by 50% by 2015. The incidence of new cases of malaria in 2015 was estimated at 214 million, of which 438,000 attributable deaths.[1] Children under 5 years of age constitute 86% of the deaths associated with this condition during this period.[2] In Gabon, the infection is endemic with an estimated inoculation rate of 33.9 infective bites per person per year.[3] The most common *Plasmodium* species in Gabon is *Plasmodium falciparum*, which is implicated in the highest number of cases of severe malaria.[4,5] In 2003, Gabon aligned his policy with the 2000 World Health Organization (WHO) recommendations for malaria management.[6] This management is based on the joint action of vector control, a well-integrated process in certain areas of the WHO African region,[4] the rapid diagnosis of plasmodium infections (interest in rapid diagnostic tests [RDTs]) and effective treatment of proven cases.

However, there are changes in the clinical profile of children with malaria. As the rate of malaria infection declines, the number of malaria cases among children not in the population

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at risk increases, the occurrence of severe malaria outside the age range of children under 5 years is becoming more common.[7,8] These data put forward increasing susceptibility to malaria in the elder child, and support the hypothesis of an epidemiological transition phase in malaria dynamics.[7,9]

Thus, at a time when the international community is preparing to meet new challenges in the fight against malaria,[1] we projected to enlighten a status for which few data are currently available, severe malaria in children over 5 years old.

The main objective of this survey was to determine the prevalence and clinical profile of severe malaria in children over 5 years old in Libreville. The secondary objectives of identifying the most frequently encountered clinical forms, to compare the profile of severe malaria in children over 5 years of age to that of children under 5 years (target population of the control program), and to describe the evolution under treatment.

MATERIALS AND METHODS

It was a prospective study, which ran from October 1, 2015, to September 30, 2016. We ran the survey in the pediatric departments of three hospitals in Libreville, randomly selected from six public hospitals. We included all children aged 0–15 years, hospitalized in one of these services, who had a positive thick blood smear and/or a positive RDT. We did not include patients aged over 15 years, patients treated for malaria without a parasitological or immunological diagnosis, cases of severe malaria whose sign of severity could be due to another associated disease.

We used the BioLINE® Malaria Antigen P.f/Pan® SD test for our investigation, which is a rapid, qualitative, and differential test. It is performed in one step, allows the detection of *P. falciparum*-specific histidine-rich protein II antigens and the pan-specific plasmodium lactate dehydrogenase antigen to other *Plasmodium* species in human blood samples. The classification of severe malaria was made if the patient had at least one of the WHO criteria of severity for malaria, criteria updated in the WHO guidelines for the treatment of malaria.[10]

It was thus possible to describe different forms of severe malaria, namely:
- Anemic form: Malaria associated with severe anemia
- Neurological form: Malaria associated with a disorder of consciousness, prostration, or multiple convulsions
- Parasitemic form: Malaria associated with hyperparasitemia
- Hemorrhagic form: Malaria associated with abnormal spontaneous bleeding
- Icteric form: Malaria associated with jaundice and visceral failure.

We managed the data obtained from Epi Info 7. The Chi-square test was used to assess differences in categorical data between groups. We used the analysis of the student's *t*-test for comparisons of means. We assessed risks with the odds ratio (OR). $P < 0.05$ was considered statistically significant.

RESULTS

During our study period, 2605 children were hospitalized in all three selected hospitals, of which 596 cases of malaria were formally identified. Of these 596 patients, 206 (34.6%) had severe malaria criteria.

The mean age was 56.1 ± 40.9 months with the extremes being 2 and 180 months. The sex ratio was 1.14 with 110 boys (53.2%) for 96 girls (46.6%).

The overall average length of hospital stay during the period was 4.3 ± 2.3 days. Children with severe malaria were hospitalized on average for 4.7 ± 2.7 days (1–18).

The distribution according to age showed:
- In cases of malaria in general ($n = 596$), children ≤5 years accounted for 63.8% ($n = 380$), children ≥5 years accounted for 36.2% ($n = 216$).
- In cases of severe malaria ($n = 206$), children ≤5 years represented 63.1% ($n = 130$) of cases, children ≥5 years were for 36.9% ($n = 76$) of cases.

The various clinical forms found in severe malaria were led by the anemic form, which represented 54.4% of the severe forms found, as shown in Figure 1.

In cases of severe malaria, children under 5 years were at:
- 66.9% ($n = 87$) of anemic type
- 23.8% ($n = 31$) of cerebral type
- 6.9% ($n = 9$) of a parasitemic type
- 2.4% ($n = 3$) other types: Icteric, hemorrhagic, or cerebral anemic.

In cases of severe malaria in children over 5 years:
- 32.9% ($n = 25$) had anemic form
- 55.3% ($n = 42$) had a neurological form
- 6.6% ($n = 5$) a parasitemic form
- 5.2% ($n = 4$) other types: Hemorrhagic, icteric.

The risk of having an anemic form when the child was <5 years old compared to a child over 5 years of age was OR = 4.13 (95% confidence interval [CI] [2.2–7.9]).

The risk of having a cerebral form when the child was more than 5 years old compared to a child who was <5 years old was OR = 3.9 (95% CI [2–8.3]).

The risk of having a parasitemic form when the child was <5 years old compared to a child over 5 years of age was OR = 1.06 (95% CI [0.3–3.8]).

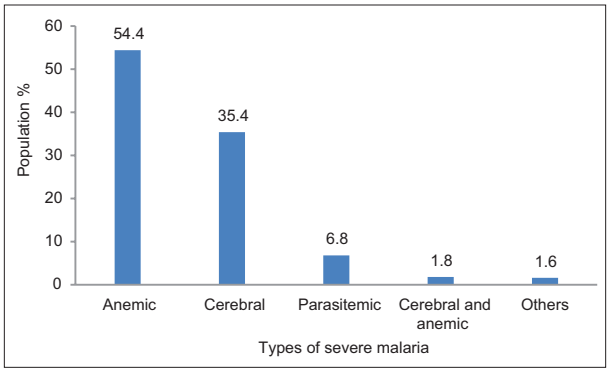

Figure 1: Distribution of severe malaria by form

The biological and clinical characteristics of the neurological form that was most important in those over 5 years of age are described in Table 1.

The outcome of the patients was marked by an absence of mortality in children >5 years. Nevertheless, 3 (0.8%) deaths related to severe forms were noted in children under 5 years.

DISCUSSION

Methodology

This study looked at severe malaria. To obtain the most representative results possible according to the WHO definition, we have voluntarily counted as simple malaria all cases of severe malaria that were associated with pathologies with the same signs of severity.[10] Thus, patients with sickle cell disease or patients with associated meningitis have been removed from anemic forms or cerebral types. Finally, the survey included cases of severe malaria whose reported severity criteria were essentially clinical, except anemia and parasitemia. The other biological criteria were not therefore systematically explored.

Age and sex of children

The analysis of the literature on child malaria shows that the average age of sick children is constantly increasing. The mean age in severe malaria cases was 25.5 ± 19.9 months in Libreville in 2005, in a cohort conducted in the same hospitals as our survey.[11] Not far from Libreville in Franceville, this average age of patients with severe forms of malaria was calculated at 48.5 ± 3.9 in 2011.[12] This finding is attributable to the benefits of the malaria control measures implemented in Gabon. This protection is for pregnant women and newborns, so younger children have been better protected.

The sex ratio was close to 1 (46.8% girls). This observation is almost the same in all comparable studies found in the literature. Sex was not a factor of severity in our series.[11,12]

Duration of hospitalization

The average duration of hospitalization was 4.3 days with extremes of 1–18 days. It was 4.7 days when it was only severe forms. This hospital stay was shorter than that reported by Lisomba Likwela which was 6 days on average. The explanation could lie in the fact that the treatment was 3 days on average with artesunate intravenous (IV) used in the structures of Gabon, as recommended by the National Program against malaria against 7 days of quinine with oral relay to the resolution of signs of gravity in Kisangani.[13]

Morbidity

This study involved 2605 hospitalized patients, of whom 596, or 22.9%, were proven cases of malaria in children aged between 0 and 15 years. The place of malaria in pediatric hospital morbidity in Gabon has remained the same; malaria is the leading cause of pediatric hospitalization.[11,12,14] However, its proportion seems to decrease with time. It was 36% of the causes of hospitalization in 2002 in Libreville before the implementation of the measures against malaria as reported by Dzeing-Ella *et al.* to 28% in 2007.[11,15] Our results are close to those of Lisomba Likwela *et al.* in the Democratic Republic of Congo (DRC) (36.3%)[14] and de Ossou-Nguiet *et al.* in Congo 34.9%.[16] Less important values were found in other authors, namely, 6.4% in Camara *et al.* in Senegal,[17] 4.37% at Gbadoé *et al.* in Togo,[18] and 14.7% at Moyen *et al.* in Congo.[19] We can explain the differences between the prevalence of malarial cases in Gabon, and those of West African countries by epidemiology. Central African countries are areas with the permanent transmission of malaria, but they are also areas with the deadly *P. falciparum* strain, while West African countries are areas where malaria and especially *P. falciparum* are less common.[4,5]

During this study, 206 cases of severe malaria cases were collected. This sample is comparable to those of Likwela *et al.* in the DRC (n = 155) and Ossou-Nguiet *et al.* in Congo (n = 396).[13,16] However, we were lower than the number of cases of severe malaria in the study of Moyen *et al.* in Congo in 2010 (n = 1506). That study included the children of the four large health facilities in Brazzaville or that of Reyburn *et al.* (n = 1855) in Tanzania which took place in 10 of the 13 health facilities in the country. This smaller population in our survey may be explained by the requirement that we have systematically performed both diagnostic tests before including or excluding a patient.[19,20]

While 34.6% of hospitalized malaria cases were severe, the remaining proportion, although classified as simple malaria still had to be treated intravenously. These were cases in which artemether-based combined therapies oral therapy was not recommended due to relative gravity. These data suggest a possible readjustment of the WHOs classification for types of malaria. This observation raises the question of adopting a model that would take into account forms classified as simple but whose management requires the use of a parenteral route. A classification model such as that proposed by Newton and Krishna in 1998, which includes, in addition to the simple and

Table 1: Characteristics of the neurological form of severe malaria according to age

Characteristics	Age ≤5 years	Age >5 years	*P*
Mean hemoglobin	7.1±2.5 [2.2–11.2]	8.6±2.3 [3.3–13.8]	<0.009
Mean parasitemia	27287±48978 [500–200000]	71540±108182 [420–474600]	<0.001
Associated pathologies			
Yes	3 (9.7%)	15 (35.7%)	0.01
No	28 (90.3%)	27 (64.3%)	
Neurologic criteria			
Seizures	19 (61.3%)	10 (23.8%)	0.001
Prostration	6 (19.4%)	15 (37.5%)	0.08
Obnubilation	3 (9.7%)	13 (31.0%)	0.02
Coma	2 (6.5%)	4 (9.5%)	0.9

severe forms of malaria, a so-called moderate intermediate form.[21]

Of these, 206 children with severe malaria, 76 (36.9%) were over the age of five. Furthermore, while there is a significant difference in the number of cases between the two age groups analyzed the burden of severe malaria on children over 5 years remains as high as in the younger population. Indeed, 36.9% of children over 5 years who were hospitalized for malaria had a severe form as described by the WHO against 63.1% in the under 5 years, the target population of the control program. This data suggest that the malaria control program should be extended to children of greater ages.

Major types

The anemic form was most frequently found in our study (over 54.4%). Anemic forms were 66.7% of cases in the patient aged <5 years. According to the literature, anemic forms are the most common forms in the stable transmission zone, and Dzeing-Ella *et al.* in 2005, as well as Lekana-Douki *et al.* in 2011, had already made the same observation in Libreville and Franceville.[11,12] This form was also in these surveys the most common in children under 5 years, with also an OR of 2 in Dzeing-Ella's inquiry. One of the explanations for this occurrence would be simple arithmetic. The younger is a child, the less he has red blood cells. Therefore, when the same number of red blood cells is lysed in a small child and in a large child, with the same inoculum of parasites, the small child will have greater anemia because he will have lost proportionately more red blood cells than the big child. This mechanism explains that the average hemoglobin level is lower in children under 5 years compared to those over 5 years of age [Table 1].

The anemic form, with 32.9% of cases, was the second most frequent severe form after neurological forms in children over 5 years old. The neurological form was the most common form of severe malaria in children over 5 years old. This form accounted for 55.3% of severe forms. The calculation of the OR showed that this category of the child was 4 times more likely to have a cerebral form that child under 5 years old. This finding was already the same in 2005 by Dzeing-Ella *et al.* in Libreville, who found that neurological forms were in the second position regardless of age group. However, this survey took place the year before the malaria program measures were implemented.[11] In the Mabiala-Babela *et al.* studied in Brazzaville (Congo) in 2002, in a study of children over 5 years old at the Brazzaville University Hospital,[22] the prevalence of anemic forms was higher (46.3%) than neurological forms (22.2%).

The children over 5 years of age in our survey were, therefore, those who have benefited from the protection provided by the Malaria Control Program, and therefore have a lower antimalarial premunition which is characterized by a higher parasitemia in the analysis of the characteristics of neurological forms according to age.[23]

Deaths

There were no deaths in children older than 5 years. This result emphasizes the good results of the management of IV arterial IV drug access. Currently, quinine is less and less used in the treatment of severe malaria in favor of artesunate.

CONCLUSION

Children over 5 years represented 36.9% of cases in severe forms, but the impact of severe malaria in this age group was equivalent to that in the younger child. The neurological form was the most frequent form found in this age group. The risk of occurrence of cerebral type was 3.9 times higher than in children under 5 years. Low mortality was the corollary of appropriate care. Thus, we observe a change in the epidemiological facies of severe malaria in our region. It, therefore, seems urgent to extend the continuum of prevention for these populations whose preemption is weakened by a vaccine-type solution. The prevention and

diagnosis of certainty, prerequisites for adequate treatment, therefore remain the most effective means of combating the mortality of severe malaria in children over 5 years of age.

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