SEVERE MALARIA IN BURKINA FASO: INFLUENCE OF AGE AND TRANSMISSION LEVEL ON CLINICAL PRESENTATION

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Abstract. We analyzed the clinical presentation of 800 severe malaria cases six months to 15 years of age (mean ± SD = 4.3 ± 3.0) recruited at the pediatric ward of the Ouagadougou University Hospital, and at the Sourou and Nayala District Hospitals in Burkina Faso. Inclusion criteria followed the World Health Organization (WHO) definition of severe and complicated malaria. The children were treated according to WHO guidelines with a complete regimen of drugs that were provided free of charge as part of the study. The case fatality rate of each sign and symptom of severe malaria was calculated on the 686 children whose outcomes were known. A total of 95 patients (13.8%) died while in the hospital; the mean ± SD age of these children was 3.2 ± 2.1 years. The age distribution and the clinical patterns of severe malaria was compared in patients from the urban areas of Ouagadougou characterized by relatively low transmission, and from rural areas where the mean inoculation rates are at least 20-fold higher. The mean ± SD age of the urban and rural patients was 4.8 ± 3.0 and 2.2 ± 1.9 years, respectively (P < 0.001). The prevalence of coma was higher in the urban subsample (53.6% versus 28.9%; P < 0.001) while that of severe anemia (hemoglobin < 5 g/dL) was higher in rural patients (47.4% versus 14.8%; P < 0.001). Our data, in line with previous results obtained comparing rural areas characterized by different inoculation rates, show that the epidemiologic context influences the clinical presentation of severe malaria.

Malaria is one of the most common causes of morbidity and mortality in sub-Saharan Africa; each year, an estimated number of 1–2.8 million persons, mostly children, die of *Plasmodium falciparum* malaria. 1 Approximately 2% of clinical attacks of malaria in African children are severe,2 and the actual global malaria control strategy3 advocates their prompt and adequate treatment as an essential measure to reduce the mortality due to the disease.

The epidemiologic profile and clinical pattern of severe malaria have been shown to vary according to the intensity of exposure in children living in rural areas of East Africa with different levels of transmission.4,5 Different levels of malaria transmission are generally expected and have been demonstrated between rural and suburban environments in Burkina Faso5,6 and elsewhere in Africa,6,9 but have not been related to different forms of presentation of the disease. The importance of studying the relationships between transmission levels, age-specific incidence, and the clinical picture of severe malaria is evident in view of the development of rational control strategies. This seems of particular importance in African cities, where a fast urbanization process alters transmission pattern of malaria, and thus, possibly its clinical and epidemiologic features. We present here the results of a comparative study that investigated the clinical presentation of severe malaria in urban and rural areas of Burkina Faso characterized by different levels of transmission.

MATERIALS AND METHODS

Study area and patients. The study was carried out during the rainy seasons of 1993 and 1994 at the 158-bed pediatric ward of the Ouagadougou University Hospital located in the central area of the city, and during the 1996 rainy season in the two District Hospitals of Sourou and Nayala Provinces in Burkina Faso. The study area is characterized by a rainy season lasting from June to October, which corresponds to the high malaria transmission season, and by a long dry season from November to May. Obvious differences exist in malaria transmission levels between urban and rural areas; Rossi and others6 and Esposito and others7 reported inoculation rates values from one to 10 per person per year in urban areas of Ouagadougou, and from 50 to 200 in the surrounding rural zones. More recently, during the 1994 high transmission season (Sirima BS, unpublished data), inoculation rates values lower than five per person per year were recorded in urban areas of Ouagadougou; in the surrounding rural areas, the extensive entomologic evaluations conducted in 1993–1994 in the frame of the large-scale trial on impregnated curtains (Habluetzel A, unpublished data) showed inoculation rates on the order of 300–500 per person per year; similar values in the same area were also recorded by Modiano and others.11 The main malaria vectors are *Anopheles gambiae, A. arabiensis,* and *A. funestus.*12 The great majority of the population belongs to the Mossi ethnic group for the Ouagadougou area and to the Samo ethnic group for the Sourou and Nayala Provinces.

The study protocol was approved by the Centre National de Lutte contre le Paludisme of the Ministry of Health of Burkina Faso. Children six months to 15 years of age were included in the study. Severe malaria was defined by the presence of *P. falciparum* in the thick blood film associated with at least one of the following condition: prostration (incapacity of the child to sit without help, in the absence of coma), unrousable coma (score between 0 and 2 on the Glasgow modified coma scale12), repeated generalized convulsions (more than two episodes in the preceding 24 hr), severe anemia (hemoglobin < 5 g/dL), hypoglycemia (< 40 mg/dL), pulmonary edema/respiratory distress, spontaneous bleeding, and renal failure (plasma creatinine > 3 mg/dL). Children with other detectable infections or cause for the clinical presentation were not included in the study. On ad-
mission and after oral informed consent of the parents was obtained, children were weighed and a blood sample was drawn for measurement of parasitemia, blood glucose level, plasma creatinine concentration, hemoglobin concentration, hematocrit, complete blood cell count, and humoral response to malaria antigens. Patients were treated according to World Health Organization\textsuperscript{14} with a complete regimen of drugs that were provided free of charge as part of the study. The clinical outcome was recorded.

Blood examination. Thick and thin blood smears were prepared following standard procedures and 100 microscopic fields (approximately 20 leukocytes/field at a magnification of 1,000 = approximately 0.25 μl of blood) of the thick blood smears were examined. The \textit{Plasmodium} species was identified on the thin blood smear.

Statistical methods. The chi-square test was used for the analysis of relative risk of signs and symptoms and for the comparison of the prevalence of each condition according to geographic origin. The Student’s t-test was used for the comparisons of age means and parasite density. Version 5 of the program Epi-Info (Centers for Disease Control and Prevention, Atlanta, GA) was used for statistical analysis.

RESULTS

A total of 800 severe malaria cases were included in the study; 707 were admitted at the Ouagadougou University Hospital, 43 and 50 at the District Hospitals of Tougan (Sourou Province) and Toma (Nayala Province), respectively. The male:female ratio was 1.22. Of 782 patients whose geographic residence was reliably traced, 81.8% came from urban areas of Ouagadougou and 18.2% from rural zones; 34.5% of the rural patients were from villages near Ouagadougou and were recruited into the study in 1993 and 1994, while the remaining 65.5% were enrolled in 1996 at the District Hospitals of the Sourou and Nayala Provinces. The majority of the patients recruited in Ouagadougou belonged to the Mossi ethnic group (82%) while in Sourou and Nayala provinces, 85% were from the Samo ethnic group. The mean ± SD age of the total sample was 4.3 ± 3.0 years; the urban children showed a higher age mean compared with rural patients (4.8 ± 3.0 versus 2.3 ± 1.9; \( P \ll 0.001 \) by Student’s \( t \)-test). The percentage age distribution of the two groups is presented in Figure 1. In the urban subsample, 25.5% of the cases were children 0–2 years of age, and 68.7% were less than six years of age; in rural areas 78.2% were 0–2 years of age and 95.1% were less than six years of age. Of the 686 children whose clinical outcomes of the disease were known, 95 (13.8%) died while in the hospital; the mean age of these children was lower than that of those who recovered (3.2 ± 2.1 versus 4.6 ± 3.1; \( P \ll 0.001 \), by Student’s \( t \)-test). No differences in the hospital case-fatality rate between urban and rural patients was recorded (13.6% versus 14.2%; \( P = 0.99 \)). The mean ± SD duration of the illness before admission and the mean ± SD duration of the hospitalization were 3.1 ± 4.7 days (range = 0–61) and 3.8 ± 2.9 days (range = 0–34), respectively, without differences according to the geographic origin of the patients. The prevalence of each sign and symptom on admission with the corresponding relative risk are presented in Table 1. As expected, no cases of renal failure were recorded in the 223 children whose plasma creatinine concentration was determined. The relative frequencies of each condition according to geographic origin are presented in Table 2. The prevalences of coma and anemia were markedly different between urban and rural patients (Table 2) and these differences also persisted after age group stratification (Figure 2). Parasite densities were higher in urban patients (\( P = 0.047 \), by Student’s \( t \)-test).

DISCUSSION

The aim of this study was the comparative evaluation of the clinical presentation of severe malaria in West African

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence on admission</th>
<th>Case fatality rate in children with known outcome</th>
<th>Relative risk (95% CI)*</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostration</td>
<td>337/800</td>
<td>42.1</td>
<td>20/292</td>
<td>6.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Coma</td>
<td>391/800</td>
<td>48.9</td>
<td>75/346</td>
<td>21.7</td>
<td>3.68</td>
</tr>
<tr>
<td>Convulsions</td>
<td>215/792</td>
<td>27.1</td>
<td>36/193</td>
<td>18.7</td>
<td>1.60</td>
</tr>
<tr>
<td>Anemia</td>
<td>158/749</td>
<td>21.1</td>
<td>28/118</td>
<td>23.7</td>
<td>2.00</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>62/789</td>
<td>7.9</td>
<td>27/54</td>
<td>50.0</td>
<td>4.72</td>
</tr>
<tr>
<td>Pulmonary edema/</td>
<td>39/800</td>
<td>4.9</td>
<td>11/34</td>
<td>32.4</td>
<td>2.51</td>
</tr>
<tr>
<td>respiratory distress</td>
<td>11/800</td>
<td>1.4</td>
<td>3/11</td>
<td>27.3</td>
<td>2.00</td>
</tr>
<tr>
<td>Spontaneous bleeding</td>
<td>0/223</td>
<td>0.0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* CI = confidence interval.
TABLE 2
Prevalence of signs and symptoms of severe malaria according to geographic origin (only children whose geographic origin was known are considered [782/800])

<table>
<thead>
<tr>
<th>Condition</th>
<th>Urban areas</th>
<th>Rural areas</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./total</td>
<td>%</td>
<td>No./total</td>
</tr>
<tr>
<td>Prostration</td>
<td>263/640</td>
<td>41.1</td>
<td>64/142</td>
</tr>
<tr>
<td>Coma</td>
<td>343/640</td>
<td>53.6</td>
<td>41/142</td>
</tr>
<tr>
<td>Convulsions</td>
<td>171/633</td>
<td>27.0</td>
<td>41/141</td>
</tr>
<tr>
<td>Anemia</td>
<td>88/596</td>
<td>14.8</td>
<td>64/135</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>46/631</td>
<td>7.3</td>
<td>14/140</td>
</tr>
<tr>
<td>Pulmonary edema/respiratory</td>
<td>30/640</td>
<td>4.7</td>
<td>8/142</td>
</tr>
<tr>
<td>Spontaneous bleeding</td>
<td>9/640</td>
<td>1.4</td>
<td>2/142</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0/202</td>
<td>0</td>
<td>0/21</td>
</tr>
<tr>
<td>Parasite density/µL</td>
<td>13,032</td>
<td></td>
<td>8,414</td>
</tr>
</tbody>
</table>

* By Student’s t-test.

Figure 2. Prevalence (%) of coma (A) and anemia (B) in four different age groups in 782 severe malaria patients coming from urban (gray bars, n = 640) or rural (solid bars, n = 142) areas of Burkina Faso. Bars show the mean ± standard error.

children living in the urban areas of Ouagadougou, Burkina Faso, and in rural zones characterized by at least a 20-fold mean increase in the level of malaria transmission. Important differences were observed in the presentation of severe malaria in relation to the residence of the patients, with the variation involving both the age profile and the clinical spectrum of the disease. Previous studies that compared severe malaria between rural areas with different levels of transmission in East Africa showed a relationship between transmission and the clinical patterns of severe malaria. This has been recently confirmed by the same investigators, who showed marked differences in age and clinical spectrum of severe malaria between five rural African sites characterized by different levels of malaria transmission. Our data confirm this association in a different geographic zone in a comparison between urban and rural zones. In areas of lower transmission (urban in our study), severe malaria tends to affect children of relatively older ages and cerebral symptoms are dominant. In high transmission zones, severe malaria affects mainly younger children and severe anemia represents the most frequent condition. The higher mean age of urban children with severe malaria could be related to the slower acquisition of clinical immunity in the urban environment as a consequence of lower levels of exposure; this would be also supported by the higher parasite density recorded in urban patients. The differences in the prevalence of coma and anemia between the two areas are associated with the level of transmission and are not age-dependent since they persist also after age stratification. As previously reported, the prevalence of severe anemia is inversely correlated with age in both epidemiologic contexts, with the decrease in the prevalence with age being evident in urban as well as in rural patients (Figure 2); conversely, the prevalence of coma was not correlated with in age in both areas.

Trape and others reported that in African cities morbidity from severe malaria remains high despite a low intensity of transmission. Snow and others recently provided evidence that there is a significant decrease in the rates of overall and cerebral malaria with increased transmission from low-to-moderate to high. Our study does not provide data on the incidence of the disease but it clearly supports the qualitative variation described between rural areas of different endemicity. The epidemiologic and clinical pattern of severe malaria in an urban environment with a low transmission intensity appears substantially different (but not less severe) when compared with a rural area with high malaria transmission. This suggests that areas with comparable transmission intensities tend to have similar presentation patterns of severe malaria irrespective of their geographic and socioeconomic setting.

The conditions in our study associated with significantly higher case fatality rates (already partially reported) were
hypoglycemia, coma, pulmonary edema/respiratory distress, anemia, and convulsions; all these signs and symptoms were found to be associated with a high case fatality rate by Marsh and others, \(^{21}\) except for severe anemia, which showed a case fatality rate of 4.7% in the Kenyan study and of 23.7% in our study. A possible reason for this discrepancy could be a difference in the frequency of blood transfusions, \(^{22}\) while the different origin of the patients of the two studies (predominantly urban in our case and rural in the Kenyan one) does not appear to be involved in the similar case fatality rate between anemic patients coming from urban and rural areas recorded in our study.

The description of the prevalence and the prognostic significance of various signs and symptoms of severe malaria in different epidemiologic settings of Burkina Faso should also contribute to the management of the disease. The awareness of the changing pattern of severe malaria based on the level of transmission is of crucial importance in identifying appropriate control measures and treatment protocols tailored for the specific local characteristics of the disease. In rural areas, the confirmed importance of severe anemia should lead to the study of appropriate means of prevention and treatment of this type of presentation of severe malaria, while in urban areas, attentions needs to be focused more on cerebral symptoms. The potential effects of the urbanization process underway in many African cities on malaria transmission, and thus on malaria morbidity, recommend that the epidemiologic and clinical spectrum of severe malaria be closely monitored in the African urban environment.

Acknowledgments: We are indebted to the pediatric and laboratory staff of the Centre Hospitalier National Yaoudaouga of Ouedougou and of the two District Hospitals of Sourou and Nayala Provinces for skilled work and collaboration. We are grateful to the personnel of the Laboratory of Parasitology of the Centre National de Lutte contre le Paludisme and particularly to Albert Yameogo personnel of the Laboratory of Parasitology of the Centre National de Lutte contre le Paludisme for continuous advice and support.

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Financial support: This work formed part of the technical assistance programme of the Italian Direzione Generale della Cooperazione allo Sviluppo to the Centre National de Lutte contre le Paludisme of the Burkina Faso Ministry of Health. The study was partially supported by the World Health Organization, Division of Control of Tropical Diseases and by the Fondazione Pasteur-Cenci Bolognetti of the University of Rome La Sapienza for continuous advice and support.

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