CLINICAL MANIFESTATIONS OF SEVERE MALARIA IN THE HIGHLANDS OF SOUTHWESTERN UGANDA

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Abstract. Epidemics of malaria have occurred in highland areas of East Africa since the 1980s, but the clinical spectrum of severe malaria in these areas has not been described. Over a 17-month period from 2001 to 2002, we assessed 117 consecutive patients admitted to Kabale Hospital in highland Uganda who met the World Health Organization 2000 criteria for severe malaria. Sixty-six persons (56.4%) were age 5 years or older, and 51 (43.6%) were under 5 years of age. Fever, vomiting, and cough were the most frequent symptoms. Hepatomegaly and splenomegaly were infrequent. Prostration was the most frequent manifestation of severe malaria in children under 5 years of age (45.1%) and persons 5 years or older (65.2%), followed by respiratory distress (29.4%) and severe anemia (19.6%) in children under 5 years, and respiratory distress (15.2%) and impaired consciousness (13.6%) in persons 5 years or older. Strictly defined cerebral malaria was uncommon (3.4%). In a multivariate regression model, children under 5 years were more likely than persons 5 years or older to present with severe anemia (OR 5.2, 95% confidence interval [CI] 1.2–21.9) and respiratory distress (OR 3.5, 95% CI 1.3–11.1) and less likely to present with prostration (OR 0.3, 95% CI 0.1–0.7) and impaired consciousness (OR 0.2, 95% CI 0.0–0.9). In highland Uganda, severe malaria often occurs in persons older than 5 years of age. “Typical” signs like splenomegaly are frequently absent, prostration is the major manifestation, and other manifestations vary in frequency according to age.

INTRODUCTION

Malaria continues to devastate sub-Saharan Africa, causing annually more than 1 million deaths of individuals under 5 years of age.1 Most cases occur in lowland areas that have stable, high malaria transmission. In these areas, children get exposed repeatedly very early in life, and severe malaria (SM) is seen most frequently in children under 5 years of age, after which age most individuals have clinical immunity to severe disease.2 In highland areas above 1600 m, in contrast, low temperatures inhospitable to the malaria vector and parasite lead to very low malaria transmission for much of the year.3,4 In the absence of repeated exposure, development of immune responses to malaria is delayed or may wane,5,6 and older children and adults are susceptible to clinical malaria.7 Since the late 1980s, repeated malaria epidemics have occurred in the highlands of East Africa.8–10 Potential contributing factors to these outbreaks include higher local temperatures, El Niño seasonal oscillation–related weather changes, increased vector abundance and/or competence, improved access of malaria “carriers” to the highlands, changes in land use, drug resistance, lack of community awareness, and inadequate antimalarial medication supplies at local health facilities.3,10–12

It is estimated that 34 million individuals are at risk for malaria in highland or “epidemic-prone” areas.13 Although thousands of children and adults develop severe malaria in highland areas, there is only anecdotal information on the spectrum of clinical manifestations of severe malaria in the highlands and how this contrasts with what seen in lowland, high-transmission areas. To date, the only published studies on the clinical manifestations of SM in highland areas have focused exclusively on cerebral malaria or anemia.14–16 Knowledge of the major clinical manifestations of severe malaria in highland areas is important to appropriate diagnosis and treatment of malaria in these areas and to assessment of clinical problems that require further research in these areas. We therefore conducted a prospective study of the clinical manifestations of severe malaria (as defined by World Health Organization [WHO] 2000 criteria) at Kabale Regional Referral Hospital (KRH), Uganda, from March 2002 to July 2003.

PATIENTS AND METHODS

Study design. This descriptive study was part of a larger study designed to describe the clinical manifestations and demographic and immunologic risk factors for SM in highland areas. All patients who fulfilled the 2000 WHO criteria for severe malaria2 and presented to KRH from March 2002 to July 2003 (included) were consecutively enrolled.

Study area. Kabale district is about 400 km southwest of Kampala in Uganda. It is bordered by Rwanda to the south and the Democratic Republic of Congo to the West and is surrounded by volcanic mountains. It is situated at an altitude of about 2,000 meters, and the altitude of the hospital’s catchment area ranges from 1,600 to 2,400 m above sea level. The Bakiga are the predominant ethnic community, and horticultural farming is their main source of livelihood. KRH, with a 250-bed capacity, is the main hospital serving Kabale district offering specialist services in all the main fields of medicine. It acts both as a primary care center and receives referral patients from the surrounding health units. Kabale is prone to seasonal malaria epidemics,4 with recent outbreaks in 1998 and 2001. In non epidemic periods, the area has extremely low malaria vector density, with estimated entomological inoculation rates of less than one infectious bite per person per year.17

Study participants. All patients admitted to KRH during the study period with a clinical diagnosis of malaria were assessed for inclusion into this study. If a peripheral blood smear was positive for asexual forms of Plasmodium falciparum parasites and the patient had one or more of the WHO 2000 criteria for severe malaria,2 the patient was included in the study after informed consent was obtained from the patient or guardian. WHO criteria (2000) are listed in Table 1. Specific definitions for the criteria include 1) prostration: un-
Hemoglobin levels were determined with a colorimeter using Drabkin’s reagent (Human Diagnostics, Wiesbaden, Germany). Urine analysis was done by dipstick (Uristix, CombiNA 9SG, Human Diagnostics). Microscopic analysis and culture were performed on all specimens with abnormal dipstick results. Cerebrospinal fluid (CSF) was obtained and examined in all study subjects with suspected cerebral malaria unless signs of increased intracranial pressure were noted, in which case the procedure was delayed. CSF was considered normal if CSF protein was < 40 mg/dL and < 10 WBCs/μL.

Thick and thin peripheral blood smears were performed to detect *P. falciparum* infection. Parasites were counted against a white blood cell (WBC) count of 200 white blood cells (WBCs) and parasite density calculated against a WBC count of 8,000/μL. One hundred fields were examined before declaring a slide negative. In patients suspected of having malaria, absence of malaria was declared after 3 consecutive negative blood smears at 8 hourly intervals.

**Medical care of patients with severe malaria.** Uganda national treatment guidelines for SM management were used for treatment. All patients were given quinine intravenously, then orally when they could tolerate oral medication, for a total of 7 days. Those with temperatures > 38.5°C were given paracetamol. Hypoglycemic patients received 1 mL/kg of 50% dextrose as a bolus infusion. Severely anemic patients (Hb < 5 mg/dL) were transfused with whole blood, 20 mL/kg, and all anemic patients received folic acid and iron sulfate. Standard nursing care was offered. A daily assessment of consciousness and documentation of further seizures was done during admission, and a full neurologic assessment performed at discharge.

**Ethical considerations.** Ethical clearance was obtained from the Institutional Review Boards of Kabale Hospital, the Uganda National Council for Science and Technology, and Case Western Reserve University/University Hospitals of Cleveland, Cleveland, Ohio. Informed consent was obtained from all fully conscious adult participants and from parents or legal guardians of minors and unconscious patients.

**Data management and statistical analysis.** Data entry was done using Epi Data 2.1a (Epi Data Association 2000, Odense, Denmark) and analyzed with SPSS version 11.5 (SPSS 2003, Chicago, IL.). Categorical variables were compared using Fischer’s exact test and continuous variables with Student’s *t* test. Odds ratios (OR) and *P* values were used as measures of significance, a *P* < 0.05 was considered significant. A multivariate logistic regression model was used to assess likelihood of specific manifestations of SM in study participants under 5 years of age as compared with those 5 years of age or older.

**RESULTS**

**Study patient characteristics.** During a 17-month study period, March 2002 to July 2003, 11,829 patients were admitted to Kabale hospital. Of the 4,957 patients with medical conditions, 1,759 were admitted to the pediatric ward and 3,198 to adult medical wards. Eight hundred eighty-two patients with medical conditions (292 pediatric and 90 adult) had symptoms consistent with malaria and had microscopy testing for *P. falciparum* infection. One hundred fifty-two of these patients (65 children under 5 and 87 patients 5 years and older) had positive smears for *P. falciparum*, of whom 120 fulfilled the criteria for SM. The other 32 patients had severe weakness and/or inability to take oral medication, but did not meet the definition of prostration, and so were excluded from the study. Two patients with SM refused consent and one with incomplete record was excluded. The remaining 117 patients constituted our study group. Forty-eight patients (41.0%) were male and 51 (43.5%) were under 5 years of age.

- **Manifestations of severe malaria in patients admitted to Kabale Hospital.**

<table>
<thead>
<tr>
<th>Manifestations of severe malaria* (WHO 2000 criteria)</th>
<th>Age ≤ 5 years</th>
<th>Age &gt; 5 years</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostration</td>
<td>23 (45.1)</td>
<td>43 (65.2)</td>
<td>0.039</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>4 (7.8)</td>
<td>9 (13.6)</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>15 (29.4)</td>
<td>10 (15.2)</td>
<td>0.072</td>
</tr>
<tr>
<td>Multiple seizures</td>
<td>5 (9.8)</td>
<td>3 (4.5)</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>Jaundice</td>
<td>5 (9.8)</td>
<td>4 (6.1)</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>Hemoglobinuria</td>
<td>1 (2.0)</td>
<td>3 (4.5)</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>Circulatory collapse</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>Abnormal bleeding</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>–</td>
</tr>
<tr>
<td>Severe anemia</td>
<td>10 (19.6)</td>
<td>3 (4.5)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

* WHO 2000 criteria.
† *P* ≤ 0.05.

Sixty-two percent of the 117 patients had received antimalarial medication prior to hospital evaluation. These drugs were obtained from small private clinics (21.2%), shops (17.8%), health centers (16.9%), a hospital (5.1%), or other sources. Chloroquine and sulfadoxine-pyrimethamine were the antimalarial medications most often used prior to hospital evaluation.

Most patients were less than 40 years of age, but there was a bimodal peak in cases from 0 to 8 years and 15 to 32 years of age, which mirrored the admission peaks for individuals evaluated for conditions other than malaria (Figure 1). Patients presented to the hospital throughout the year with peaks between November and January, and June to August (Figure 2).

**Clinical features.** The median duration of illness was 4 (inter quartile range [IQR], 3–7) days, and this did not differ significantly between children under 5 years and individuals 5 years and older. Most individuals had received antimalarial medication prior to admission (60.8% of children under 5 years, 62.1% of individuals 5 years and older). Fever was the most commonly reported symptom (Table 2) and in almost all cases marked the onset of illness.

**Respiratory system.** Cough was frequently present in individuals with severe malaria, particularly children under 5 years of age (Table 2). However, the presence of cough was...
not associated with an increased frequency of respiratory distress, which was present in 23.9% of individuals with cough and 17.9% of individuals without cough \((P = \text{NS})\). Respiratory distress was termed mild if age-related tachypnea with nasal flaring was seen, and severe if deep/acidotic breathing or subcostal retractions were seen. Overall, respiratory distress was more common in children under 5 years than older children and adults (29.4% versus 15.2%, \(P = 0.07\)). Subcostal retractions and crackles on lung exam were rare physical findings (7.7% and 3.4%, respectively), suggesting that cough was not related to pneumonia in etiology. Although respiratory distress was also more frequent among patients with severe anemia (20.0% versus 8.6%), this difference was not statistically significant, \(P = 0.14\).

**Gastrointestinal system.** Vomiting and diarrhea were common symptoms in children under 5 years (61.2% and 38.8%, respectively) and individuals 5 years and older (61.8% and 32.4%), respectively.

**Central nervous system (CNS).** CNS involvement included seizures, prostration, impaired consciousness, coma, abnormal postures and deep tendon reflexes, and brain stem abnormalities with evidence of raised intracranial pressure. Altered consciousness occurred in 11.1% of all patients (7.8% of children under 5 years, 13.8% of individuals older than 5 years).
During the 17-month period of this study, mor-
a. – (3.4%) and hypoglycemia (3.4%), and only

0.009, Student
As compared with individuals 5 years
– P=
2
4
The
N
test (parasite density data log-transformed).
Eight patients had de-compensated
°
†
‡
Signs on physical exam
Temperature °C, mean (SD)
38.5 (1.6) 37.8 (1.1) 0.01
Jaundice
5 (9.8) 4 (6.1) > 0.1
Hepatomegaly
11 (21.6) 7 (10.6) > 0.1
Palpable spleen
8 (15.7) 2 (3.0) 0.02
Respiratory distress
15 (29.4) 10 (15.2) 0.07
Mild
5 (9.8) 2 (3.0) > 0.1
Severe
10 (19.6) 8 (12.1) > 0.1
Altered consciousness
4 (7.8) 9 (13.6) > 0.1
Abnormal postures
1 (2.0) 2 (3.0) > 0.1
Abnormal tendon reflexes
3 (5.9) 12 (18.2) 0.06

* X² test.

years). Abnormal posturing (decorticate, decerebrate, or
opisthotonus) was seen in only three patients, of whom two in
addition had irregular respiration. Three patients had neck
stiffness and one had abnormal pupillary reflexes and absent
conical reflexes. Abnormal deep tendon reflexes were more
frequent in individuals older than 5 years as compared with
children under 5 years (18.8% as compared with 5.9%, P =
0.04, Table 2). Seizures were reported in only 15 (12.8%)
patients at the time of admission, and only three patients had
further seizures witnessed during the course of the admission.

Cardiovascular system. Eight patients had de-compensated
anemia with features of cardiac failure. These patients
improved clinically after blood transfusion. No other patients
presented with features of circulatory decompensation.

Genitourinary system. Twenty-two percent of patients had
trace proteinuria on urine dipstick testing, but none had > 1 +
proteinuria. Four (3.4%) patients had hemoglobinuria, of
whom three had red blood cells seen on microscopy. In all
three of these patients, the microscopic hematuria cleared
within two days. One patient had a serum creatinine of 3.5
mg/dL, but never developed oliguria and improved on anti-
malarial medication.

Laboratory findings. As compared with individuals 5 years
and older, children under 5 years had lower mean hemoglobin
and blood glucose but a higher geometric mean parasite den-
sity (Table 3). Overall, most patients had low parasite densi-
ties; 60 (51.3%) had a parasite density of < 20,000/μL (< 0.4%),
and only 7% had densities > 100,000/μL. We were
only able to perform blood glucose tests in 86 patients. Hy-
poglycemia (blood glucose < 40 mg/dL) was uncommon
occurring in only 4/86 (4.7%). Gametocytes were seen in 16.1%
of the patients. Neither prior antimalarial drug therapy nor
the duration of illness had any significant effect on the preva-
ience gametocytes.

Manifestations of severe malaria in a highland area. The
most common manifestations of severe malaria as defined by
the WHO 2000 criteria were prostration in 66 (56.4%), respi-
ratory distress in 25 (21.4%), severe anemia 13 (11.1%), im-
paired consciousness in 13 (11.1%), jaundice in 9 (7.7%), and
multiple seizures in 8 (6.8%) patients (Table 3). Individuals
older than 5 years more commonly had prostration than chil-
dren under 5 years (68.2% as compared with 45.1%, P =
0.039), while children under 5 years of age were more likely
than individuals over 5 years to present with respiratory dis-
tress (29.4% as compared with 15.2%, P = 0.07) and severe
anemia (19.6% as compared with 4.5%, P = 0.016). Multi-

TABLE 2
Clinical symptoms and signs of individuals admitted for severe
malaria

<table>
<thead>
<tr>
<th>Age ≤ 5 years</th>
<th>Age &gt; 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 51)</td>
<td>(N = 66)</td>
</tr>
<tr>
<td>Fever</td>
<td>50 (98)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31 (60.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (37.3)</td>
</tr>
<tr>
<td>Cough</td>
<td>36 (70.6)</td>
</tr>
<tr>
<td>Difficult breathing</td>
<td>18 (35.2)</td>
</tr>
<tr>
<td>Seizures</td>
<td>7 (13.7)</td>
</tr>
</tbody>
</table>

TABLE 3
Laboratory findings in individuals admitted with severe malaria

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Age ≤ 5 years (N = 51)</th>
<th>Age &gt; 5 years (N = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>7.2 (2.5)</td>
<td>9.4 (2.1)</td>
</tr>
<tr>
<td>Leukocyte count/μL</td>
<td>6,494 (5,543)</td>
<td>7,553 (9,959)</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>103 (26)</td>
<td>125 (68)</td>
</tr>
<tr>
<td>Parasite density/μL (geometric mean)</td>
<td>18,357</td>
<td>9,990</td>
</tr>
<tr>
<td>Gametocytes/200 leukocytes</td>
<td>8 (15.7)</td>
<td>11 (16.7)</td>
</tr>
</tbody>
</table>

* Student’s t test (parasite density data log-transformed).
† N = 86.

There was a strikingly low prevalence of strictly defined
cerebral malaria* (3.4%) and hypoglycemia (3.4%), and only
one child had hyperparasitemia. Circulatory collapse, abnor-
mal bleeding, and pulmonary edema were not seen. Multiple
(two or more) manifestations of severe malaria were seen
more frequently in children under 5 years than in individuals
5 years or older (52.9% as compared with 30.3%, P = 0.022).
In children younger than 5 years, the most common paired
manifestations were prostration and respiratory distress (17.6%)
and prostration and severe anemia (9.8%), while in individu-
als 5 years and older, prostration and respiratory distress
(13.6%) and prostration and jaundice (4.5%) were the most
common paired manifestations. Patients with severe anemia
had a longer duration of illness before presentation to the
hospital, 9.3 versus 5.4 days (P = 0.009, Student’s t test).

Outcome. During the 17-month period of this study, mor-
tality for patients with severe malaria was very low. Only two
patients (1.7%) died, both within 24 hours of admission, from
cerebral malaria. The two patients who died were a 7-month-
old boy who presented with multiple seizures, deep coma,
respiratory distress, and hyperparasitemia, and a 13-year-old
girl who presented with respiratory distress, multiple gener-
alized seizures, deep coma, hypertonia, and hyporeflexia.

TABLE 4
Relative risk of specific manifestations of severe malaria (SM) for
individuals under 5 years of age as compared to individuals 5 years
and older in Kabale Hospital, Uganda

<table>
<thead>
<tr>
<th>Manifestations of SM</th>
<th>Adjusted OR (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe anemia</td>
<td>5.2 (1.2–21.9)</td>
<td>0.025</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>3.8 (1.3–11.1)</td>
<td>0.016</td>
</tr>
<tr>
<td>Prostration</td>
<td>0.3 (0.1–0.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>0.2 (0.0–0.9)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

* Multivariate logistic regression analysis including all 10 WHO criteria.
Morbidity was also low. The only patient with significant neurologic sequelae was a 30-year-old lady with hypoglycemia, impaired consciousness, respiratory distress, hypotension, and hyperekplexia who developed ataxia after regaining consciousness and was still ataxic at discharge.

DISCUSSION

The current study is the first to describe the different clinical manifestations of severe malaria in highland East Africa and documents a clinical spectrum of malaria distinct from that seen in malaria holoendemic areas or other areas of unstable transmission. In this epidemic-prone highland area of Uganda, a bimodal peak in cases of severe malaria was seen at ages 0–8 years and ages 15–32 years, in contrast to the usual single peak at ages 0–4 years in malaria holoendemic areas. The clinical picture of malaria also differed in important ways from that described previously, whether in areas of stable or unstable transmission. Prostration, and not cerebral malaria or severe anemia, was the most common manifestation of severe malaria; strictly defined cerebral malaria was rare (though impaired consciousness was not); and cough was a very frequent symptom, particularly in younger children. As in previous studies, the major clinical manifestations of severe malaria presented in an age-related fashion: prostration and impaired consciousness were more frequent in individuals older than 5 years, while respiratory distress and severe anemia were more frequent in children 5 years and under. However, for all major clinical manifestations except severe anemia, there was significant overlap between age groups.

The bimodal age peak for severe malaria seen in this study has not, to our knowledge, been previously described. 56% of severe malaria cases occurred in children from 0 to 8 years of age, and 29% in individuals from 15 to 32 years of age. Thus, 85% of all cases of severe malaria occurred in these two age ranges. The complete lack of cases in individuals between the ages of 45 and 60 suggests a degree of immunity to severe disease in older adults (> 40 years) in this population. A small third “peak” of four cases was seen in individuals over the age of 70 years and may reflect a waning of immunity in older age or malaria as a complication of other underlying illness or debilitation in this age group. The adult to child ratio (ratio of individuals with disease ≥ 15 years to those < 15 years), which is commonly used to define the community-wide level of antimalaria immunity in outbreak-prone areas, was 0.65 for individuals with severe disease and 1.15 for outpatients with uncomplicated malaria (unpublished observation), suggesting that individuals above 14 years of age in this population are more strongly protected against severe than mild malaria. Interestingly, very few cases of malaria were seen in children ages 9–14 years (6 cases, 5.1%), and when all admissions were analyzed, the same peaks from 0 to 8 years and 15 to 32 years were seen, with a drop in admissions for ages 9 to 14 years (Figure 2). In a review of malaria morbidity in areas of differing transmission, Snow and others estimated malaria attack rates in areas of stable, high transmission of 1, 0.25, and 0.4 per 1,000 persons per year in individuals aged 0–4, 5–14, and 15 years or older, suggesting that even in these areas, children aged 5–14 have lower frequencies of malaria attacks than adults. The reason for these age-related peaks and decreases in disease is unclear. In the current study area, potential reasons for the decrease in cases among children 9–14 years of age include the development of some degree of antimalarial immunity in childhood that wanes during adolescence and the attendance of some children in this age group at boarding schools in other areas. However, neither of these reasons seem sufficient to fully explain the lower frequency of cases in this age group. The presence of a second peak from ages 15 to 32 years in our study argues for new susceptibility factors in this age group, though the nature of these factors is unknown. HIV infection, which occurs most frequently in the 15–32 year age range, could be a potential explanation for part of the increase in admissions in this age group. HIV infected persons develop symptomatic malaria more frequently than HIV noninfected persons and may also develop severe malaria more frequently. In the current study, HIV status was not routinely tested because of the lack of freely available counseling, testing, or medications for HIV at the time of the study and inadequate study funding for provision of these interventions. No patient had clinical signs of AIDS. Lack of testing for HIV infection was a weakness of the present study, and in future studies we hope to assess the contribution of HIV to severe malaria in this population.

Prostration was by far the most common manifestation of severe malaria in all age groups. Although prostration has been described in similar frequencies in other areas of Africa with high and low malaria transmission, most large studies of severe malaria have not included assessment of the frequency of prostration. A “supporting” criterion in the WHO 1990 severe malaria definition but a defining criterion in the WHO 2000 definition, prostration appears to have a lower case fatality rate than some other manifestations of severe malaria (6.8–8.2% in Burkina Faso and Ghana). However, because it is the main reason for hospital admission for patients with malaria in highland Uganda, it will be important to educate health care workers in this area about the characteristics and frequency of this presentation of severe malaria. Very little has been written about the pathogenesis of prostration in severe malaria, and although it is considered by some a sign of CNS disease, the mechanisms by which malaria leads to inability to sit, stand or feed are poorly understood.

The age-related differences in specific clinical manifestations are likely due to multiple factors, including differential parasite organ sequestration in younger children as compared with older children and adults, low levels of complement regulatory proteins leading to increased red cell destruction in young children, inadequate reticuloocyte production in young children, and possibly the need for exposure to specific strains in cerebral malaria. The almost complete lack of cerebral malaria in this population was striking, since cerebral malaria has been described as a frequent complication in other areas of unstable transmission, including a highland area of Kenya. There are a number of possible explanations for this difference. A majority of patients in the current study received antimalarial treatment prior to hospital admission, and this may have decreased parasite load and risk of CNS complications. Hyperparasitemia was rare in the current study (< 1%) but common in the Kenyan study. Alternatively, a higher level of antidepalse immune in this highland community or a paucity of “cerebral malaria strains” of P. falciparum in nonepidemic periods in this community may have led to the low frequency of cerebral malaria cases in this area.
Cough was a common symptom of malaria in this community, occurring in frequencies higher than those reported in other studies. In addition, respiratory distress was a common manifestation of severe malaria, particularly in younger children. Studies have documented airflow and gas transfer abnormalities in individuals with malaria, particularly those with respiratory symptoms, and several studies have documented overlap between pneumonia and malaria diagnoses when WHO Integrated Management of Childhood Illness (IMCI) guidelines are used in malaria endemic areas. Only a few individuals in the current study with signs of respiratory distress had crackles on auscultation, and all but one recovered without antibiotic treatment. Thus their pulmonary signs and symptoms were likely due to malaria alone.

Outcome in patients with severe malaria over the seventeen-month period was excellent, with a very low mortality rate (2 of 117 individuals, 1.7%) and little long-term morbidity. There are several possible reasons for this. First, no epidemic occurred during this time period, so hospital resources were not overwhelmed and overall severity of disease may have been lower. Second, most patients were treated with antimalarial medications as outpatients, which may have decreased parasite burden and reduced the risk of complications. Third, the frequency of cerebral malaria, which has a high case fatality rate, was very low, and some of the other manifestations with high case fatality rates (e.g., circulatory collapse, abnormal bleeding, pulmonary edema) were not seen. Fourth, this community is exceptional in its commitment to getting sick patients to the hospital, even from very far distances. In addition, the use of WHO 2000 definition likely led to inclusion of less severely ill patients and a lower case fatality rate than if the WHO 1990 definition had been used. Nonetheless, more than half the patients seen did have manifestations associated with case fatality rates of 9–37% in other studies, and the low mortality rates even in these patients suggests that good clinical care was an important factor in the excellent outcome of these patients.

The findings of the current study emphasize the importance of carefully defining clinical characteristics in areas of differing malaria transmission and provide important baseline information about how severe malaria presents in an epidemic-prone highland area. Future studies will focus on the relationships between immune responses to \textit{P. falciparum} and the different clinical manifestations of malaria in this highland area.

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REFERENCES


MANIFESTATIONS OF SEVERE MALARIA IN HIGHLANDS


