Burden, Features, and Outcome of Neurological Involvement in Acute Falciparum Malaria in Kenyan Children

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Context  Plasmodium falciparum appears to have a particular propensity to involve the brain but the burden, risk factors, and full extent of neurological involvement have not been systematically described.

Objectives  To determine the incidence and describe the clinical phenotypes and outcomes of neurological involvement in African children with acute falciparum malaria.

Design, Setting, and Patients  A review of records of all children younger than 14 years admitted to a Kenyan district hospital with malaria from January 1992 through December 2004. Neurological involvement was defined as convulsive seizures, agitation, prostration, or impaired consciousness or coma.

Main Outcome Measures  The incidence, pattern, and outcome of neurological involvement.

Results  Of 58,239 children admitted, 19,560 (33.6%) had malaria as the primary clinical diagnosis. Neurological involvement was observed in 9,313 children (47.6%) and manifested as seizures (6,563/17,517 [37.5%]), agitation (3,161/11,193 [2.8%]), prostration (3,223/15,643 [20.6%]), and impaired consciousness or coma (2,129/16,080 [13.2%]). In children younger than 5 years, the mean annual incidence of admissions with malaria was 2694 per 100,000 persons and the incidence of malaria with neurological involvement was 1156 per 100,000 persons. However, readmissions may have led to a 10% overestimate in incidence. Children with neurological involvement were older (median, 26 [interquartile range {IQR}, 15-41] vs 21 [IQR, 10-40] months; P < .001), had a shorter duration of illness (median, 2 [IQR, 1-3] vs 3 [IQR, 2-3] days; P < .001), and a higher geometric mean parasite density (42.0 [95% confidence interval {CI}, 40.0-44.1] vs 30.4 [95% CI, 29.0-31.8] × 10³/µL; P < .001). Factors independently associated with neurological involvement included past history of seizures (adjusted odds ratio [AOR], 3.50; 95% CI, 2.78-4.42), fever lasting 2 days or less (AOR, 2.02; 95% CI, 1.64-2.49), delayed capillary refill time (AOR, 3.66; 95% CI, 2.40-5.56), metabolic acidosis (AOR, 1.55; 95% CI, 1.29-1.87), and hypoglycemia (AOR, 2.11; 95% CI, 1.31-3.37). Mortality was higher in patients with neurological involvement (4.4% [95% CI, 4.2%-5.1%] vs 1.3% [95% CI, 1.1%-1.5%]; P < .001). At discharge, 159 (2.2%) of 7281 patients had neurological deficits.

Conclusions  Neurological involvement is common in children in Kenya with acute falciparum malaria, and is associated with metabolic derangements, impaired perfusion, parasitemia, and increased mortality and neurological sequelae. This study suggests that falciparum malaria exposes many African children to brain insults.
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METHODS

Study Design

Records were reviewed of all children younger than 14 years admitted to Kilifi District Hospital with a parasitological diagnosis of malaria over a 13-year period from January 1992 through December 2004. Clinical and laboratory features of patients with and without neurological involvement on admission were compared.

Study Area

Kilifi District Hospital is located on the coast of Kenya and admits approximately 5000 children annually. It serves a predominantly rural population and is the only hospital that admits very sick children from the surrounding communities. The entomological inoculation rate (the number of times an individual is bitten by mosquitoes infected with P. falciparum in 1 year) in the catchment area ranges from less than 1 to 120 infectious bites per year.9 The area has been described in detail elsewhere.10

Study Population

Eligible children had asexual forms of P. falciparum parasites detected on blood films with malaria as the only or main diagnosis. Neurological involvement8 was defined as 1 or more of the following: (1) history of convulsive seizures during the presenting illness reported by the parent or observed at admission to the hospital; (2) the presence of agitation (abnormally high level of activity or irritability); (3) prostration (inability to sit upright or breastfeed);12 (4) impaired consciousness (Blantyre coma score <5);11,12 or coma (unable to localize a painful stimulus [ie, cerebral malaria]).11,12 We included prostration as a neurological feature because it is difficult to differentiate neurological and severe systemic causes of prostration in children.

Admission Procedures and Inpatient Care

Admission data were collected on standardized proformas that had a conserved basic format and otherwise varied according to ongoing clinical studies. The proformas detailed the medical history and the physical examination.13 The parents or guardians of children in the study consented for the clinical data to be used for epidemiological surveillance and the study of the pathogenesis of severe malaria. This study was approved by the scientific and ethical committees of the Kenya Medical Research Institute.

Emergency resuscitation and inpatient care was provided according to standard protocols.14,15 Severe malaria was treated with parenteral quinine or artemether until patients could tolerate oral medication when antimalarial therapy was completed with a full course of first-line drugs according to the national guidelines in Kenya. Those with life-threatening features were closely monitored in the high-dependency unit (ie, monitoring of patients on the unit is performed more often than in a general ward). Nursing staff performed clinical assessments of vital signs, seizures, and level of consciousness every 4 to 6 hours. Physicians’ reassessments were at 4 and 24 hours after admission and then daily. Mechanical ventilation was not available. Patients without life-threatening features (impaired consciousness, repeated seizures, or respiratory distress)2 had daily assessments on the general ward.

Laboratory Procedures

At admission, blood was drawn for a full blood cell count, glucose level, thick and thin films (stained for malaria parasites with 10% Giemsa [BDH Lab Supplies, Poole, England]); starting in 1998, routine blood cultures were performed.16 Among those patients with life-threatening features, a venous sample was drawn for acid base status and plasma electrolyte level. Metabolic acidosis was defined as a base deficit of more than 8. Hypokalemia was defined as a plasma potassium level of less than 3 mEq/L, hyperkalemia as potassium level higher than 5 mEq/L, and hyponatremia as a sodium level of less than 135 mEq/L. Lumbar punctures were performed according to a standard protocol to exclude pyogenic meningitis.17 A cerebrospinal fluid leukocyte count of up to $10 \times 10^9/L$ was considered normal.18 All tests including the parasitological diagnosis of malaria are performed in a certified research laboratory with a system for regular internal and external audits.

Data Management and Statistical Analysis

Admissions were classified as being free of neurological involvement or as having neurological involvement. The mean incidence of all malaria admissions was determined in a defined study area using population denominators projected from the Kenyan government census for 1989 (1992-1998) and for 1999 (2000-2004). The yearly population estimate was calculated from the intercensal population growth rate of 2.9% between the censuses.19,20

To describe features associated with neurological involvement, clinical characteristics at admission for the 2 groups of patients were compared and a $P$ value of less than .05 was considered statistically significant. Comparisons were performed only for patients for whom data was available. Categorical variables were compared using the Pearson $\chi^2$ test. For approximately normally distributed data, means were compared with the $t$ test. The Wilcoxon rank sum test was used for skewed data.

Multivariable logistic regression analysis was performed with neurological involvement as the dependent variable to identify features independently associated with it. In building the multiple regression model, clinical and laboratory features were included with...
**RESULTS**

**Burden of Malaria With Neurological Involvement**

A total 58,239 children were admitted to Kilifi District Hospital during the study period. Of these, 22,441 had malaria as primary diagnosis and included in analysis (FIGURE 1). The peak incidences of malaria and malaria with neurological involvement (3794 and 1181 per 100,000 persons, respectively) were in the first year of life. A marked decline in incidence was observed in children older than 5 years. The incidence of admission in children aged 5 to 9 years was 344 per 100,000 persons for malaria and 120 per 100,000 persons for malaria with neurological involvement; for children aged 10 to 14 years, the incidence of admission was 39 per 100,000 persons and 9 per 100,000 persons, respectively.

Readmissions due to malaria during the whole study period were not excluded, which could have led to an overestimation of the incidence. The proportion of children who could have had readmissions for malaria were estimated using data for children admitted between mid April 2002 and December 2004, which is when each child received a unique identification number that was used during all subsequent admissions. Using this identifier, 348 (10.2%) of 3421 children were found to have had more than 1 admission. Therefore, about 10% of the incidence data provided herein may be an overestimate contributed by readmissions with malaria.

Seizures were not common among children younger than 5 years of age, but increased in frequency with increasing age and were more likely to have severe neurological involvement (3794 and 1181 per 100,000 persons, respectively) in children older than 5 years. Seizure incidence per 100,000 persons was 48.6% among patients aged 10 to 14 years. The majority of these past seizures were associated with febrile illnesses including respiratory tract infections and malaria.

Sixty percent of patients with prostration reported a seizure. The clinical risk factors for prostration were examined among 2967 consecutive children admitted with seizures. Prostration was associated with higher parasitemia. Seizures (adjusted odds ratio [AOR] 2.44; 95% confidence interval [CI], 2.04-2.93; P < .001), delayed capillary refill time (AOR, 5.24; 95% CI, 3.72-7.38; P < .001), hypoglycemia (AOR, 3.85; 95% CI, 2.73-5.43; P < .001), metabolic acidosis (AOR, 1.92; 95% CI, 1.61-2.29; P < .001), and high parasite density (AOR, 1.01; 95% CI, 1.00-1.10; P = .999) were independently associated with prostration.

Impaired consciousness was associated with seizures, older age, higher parasite density, hypoglycemia, and acidosis but not with hyponatremia (Table 2). Patients with seizures and normal consciousness on admission had

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*Neurological Involvement on Admission* Seizures were the most common neurological feature of acute falciparum malaria and were reported or observed at admission in 37.5% of children (TABLE 1). Seizures were not common before the age of 6 months. After 12 months, the age-specific prevalence increased rapidly reaching a peak prevalence of 48.6% among patients aged 27 to 33 months. Patients with seizures had a shorter duration of illness and higher parasitemia (TABLE 2). Multiple seizures were common with 56% of those with a history of seizures reporting 2 or more episodes during the illness. In 22% of children, seizures lasted longer than 30 minutes, fulfilling the definition of status epilepticus.

During the course of inpatient stay, seizures were observed in 13.3% of children with neurological involvement. These were not associated with hypoglycemia or hyponatremia. Temperature appeared to influence seizure manifestation; 63% of generalized seizures were reported in febrile children compared with 54% secondarily generalized seizures and 44% focal seizures (χ² for linear trend = 7.2; P = .007). The recurrence of seizures in the ward was associated with increased mortality (12.8% vs 1.2%; P < .001).

Among 6212 children about whom the presence or absence of seizures during previous illnesses was known, a history of seizures was more common among those admitted with seizures (41.5%) compared with those admitted without seizures (15.1%) (P < .001). The majority of these past seizures were associated with febrile illnesses including respiratory tract infections and malaria.

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**Figure 1. Children Admitted With Malaria to Kilifi District Hospital From 1992 to 2004**

- 58,239 Children Aged <14 лет Admitted to Kilifi District Hospital Between January 1992 and December 2004
- 22,441 Had Positive Malaria Blood Test Result
- 2881 Excluded (Primary Illness Not Malaria)
- 19,560 Had Malaria as Primary Diagnosis and Included in Analysis
- 37,986 Excluded (Negative Malaria Blood Test Result)
fewer metabolic derangements compared with those with impaired consciousness. Comatose patients had been ill for a longer period prior to admission compared with those with agitation or prostration.

Overlap between the features of neurological involvement was common, particularly seizures and prostration or seizures and impaired consciousness (Table 2). All patients with agitation had at least 1 other feature of neurological involvement (ie, seizures, prostration, or impaired consciousness).

Deterioration in consciousness during admission was observed in 219 (14.3%) of 1533 children with neuro-

Figure 2. Incidence of All Malaria Admissions and Malaria With Neurological Involvement in Children by Age Group in Kilifi District Hospital From 1992 to 2004

Y-axes in blue indicate incidence range of 0 to 800 per 100,000 population.

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logical involvement admitted to the high-dependency unit. It was associated with recurrence of seizures and abnormal motor posturing but not duration of illness, admission temperature, parasite density, hypoglycemia, metabolic acidosis, hyponatremia, or severe anemia. However, secondary deterioration in consciousness was associated with higher mortality than established impaired consciousness (38.6 vs 12.8%; \( P < .001 \)). Some children developed agitation during the course of the admission. This was associated with worsening level of consciousness and increased mortality.

**Factors Associated With Neurological Involvement in Falciparum Malaria**

Children with neurological involvement were older (median age, 26 [interquartile range {IQR}, 15-41] vs 21 [IQR, 10-40] months; \( P < .001 \)), had a shorter duration of illness (2 [IQR, 1-3] vs 3 [IQR, 2-3] days; \( P < .001 \)), and a higher geometric mean parasite density (42.0 [95% CI, 40.0-44.1] vs 30.4 [95% CI, 29.0-31.8] \( \times 10^5/µL; P < .001 \) (Table 3). The majority of children admitted to the hospital with fever lasting less than 2 days had neurological involvement (65.4% vs 34.6%; \( P < .001 \)). Apart from seizures, medical history in the 2 groups was similar. Features of shock or impaired perfusion and metabolic acidosis were associated with neurological involvement. Vomiting, diarrhea, and cough were less common in patients with neurological involvement. Additional diagnoses, particularly respiratory tract infections, were less common among children with neurological involvement.

Overall, 15.3% of patients had severe anemia (hemoglobin < 5 g/dL). There was no clear association between the hemoglobin concentration and level of consciousness (Table 2). Although neurological involvement was observed at low levels of parasitemia, the proportion with neurological involvement increased with rising parasitemia: neurological involvement was present in 40% of patients with parasite densities lower than 100 \( \times 10^5/µL \), 50% of patients with densities between 100 \( \times 10^5/µL \) and 500 \( \times 10^5/µL \), and in more than 60% of those with densities higher than 1000 \( \times 10^5/µL \) (\( \chi^2 \) for trend = 120; \( P < .001 \)).

Among patients with life-threatening features, the most common biochemical derangements were hypotremia, acidosis, hyperkalemia, hypoglycemia, and elevated plasma creatinine level (Table 3). Only metabolic acidosis, hypoglycemia, and hyperkalemia were significantly associated with neurological involvement.

**Factors Independently Associated With Neurological Involvement**

Clinical and laboratory features associated with neurological involvement on univariate analysis with a \( P \) value of less than .10 (Table 3) were entered in

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**Table 1. Neurological Involvement in Children With Falciparum Malaria at Admission to the Hospital and Treatment Outcome, 1992-2004**

<table>
<thead>
<tr>
<th>No. of Cases/ Total No. of Patients Assessed (%)</th>
<th>No. (%) Who Died (n = 542)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neurological involvement at admission</td>
<td>10.247/19,560 (52.4)</td>
</tr>
<tr>
<td>Type of neurological involvement at admission</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>6,663/17,517 (37.5)</td>
</tr>
<tr>
<td>Agitation</td>
<td>316/11,193 (2.8)</td>
</tr>
<tr>
<td>Prostration</td>
<td>3,223/15,643 (20.6)</td>
</tr>
<tr>
<td>Impaired consciousness or coma</td>
<td>2,129/16,080 (13.2)</td>
</tr>
</tbody>
</table>

*Categories are not mutually exclusive (ie, some children had both seizures and agitation or other combinations).

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**Table 2. Clinical, Hematological, and Biochemical Factors Associated With Changes in Consciousness**

<table>
<thead>
<tr>
<th>Normal Consciousness</th>
<th>Seizures</th>
<th>Agitation</th>
<th>Prostration</th>
<th>Impaired Consciousness or Coma</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (Total No. of Patients)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), mo</td>
<td>22 (10-41)</td>
<td>25 (14-38)</td>
<td>24 (12-42)</td>
<td>27 (15-43)</td>
</tr>
<tr>
<td>Seizures</td>
<td>39/1395(36.8)</td>
<td>72/1460(37.7)</td>
<td>78/1460(39.7)</td>
<td>81/1570(52.0)</td>
</tr>
<tr>
<td>Duration of illness, median (IQR), d</td>
<td>3 (1-3)</td>
<td>2 (1-3)</td>
<td>1 (1-3)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Admission temperature, mean (SD), °C</td>
<td>38.6 (2.1)</td>
<td>38.7 (1.2)</td>
<td>38.2 (1.3)</td>
<td>38.0 (1.4)</td>
</tr>
<tr>
<td>Delayed capillary refill time</td>
<td>212/4880 (4.5)</td>
<td>98/2724 (3.6)</td>
<td>56/291 (19.2)</td>
<td>336/2351 (15.6)</td>
</tr>
<tr>
<td>Parasite density, geometric mean (95% CI), ( \times 10^5/µL )</td>
<td>36.5 (33.4-39.8)</td>
<td>42.2 (39.2-45.4)</td>
<td>38.8 (29.8-42.8)</td>
<td>42.6 (38.6-46.9)</td>
</tr>
<tr>
<td>Hemoglobin, mean (SD), g/L</td>
<td>77 (28)</td>
<td>95 (31)</td>
<td>86 (36)</td>
<td>100 (33)</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>735/2007 (36.6)</td>
<td>466/1366 (54.1)</td>
<td>101/182 (55.0)</td>
<td>955/1665 (57.4)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>50/1917 (2.6)</td>
<td>82/1236 (6.6)</td>
<td>22/147 (15.0)</td>
<td>330/1720 (17.6)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>102/1922 (53.4)</td>
<td>696/1236 (56.3)</td>
<td>81/157 (51.6)</td>
<td>94/1724 (54.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IQR, interquartile range.
*Unless otherwise indicated. \( P < .001 \).
†\( P < .01 \).
‡\( P < .05 \).
§Indicates when refill time is greater than 2 seconds.
a logistic regression model to identify those features independently associated with neurological involvement. Factors independently associated with neurological involvement included past history of seizures (AOR, 3.50; 95% CI, 2.78-4.42), fever lasting 2 days or less (AOR, 2.02; 95% CI, 1.64-2.49), delayed capillary refill time (AOR, 3.66; 95% CI, 2.40-5.56), acidosis (AOR, 1.55; 95% CI, 1.29-1.87), and hypoglycemia (AOR, 2.11; 95% CI, 1.31-3.37). An additional diagnosis (comorbidity) and severe anemia were independently associated with the absence of neurological involvement (TABLE 4).

**Outcome**

The median duration of hospital stay including deaths was 3 (IQR, 2-4) days and was similar in patients with and without neurological involvement overall. However, compared with those without any alteration of consciousness, patients with impaired consciousness stayed longer in the wards (3 [IQR, 2-4] vs 2 [IQR, 1-4] days; P=.001).

**Mortality**

Overall, 542 children died. Of those who died, 412 (76.0%) had neurological involvement and 130 (24.0%) did not. Mortality increased with lower levels of consciousness at admission (Table 1). Children with cerebral malaria had the highest mortality, especially those admitted without a history of seizures (22.2% vs 13.6%; P=.006). Respiratory arrest, often associated with brainstem signs, occurred more commonly in children with neurological involvement (37.2% vs 18.2% of all deaths; P=.03) while cardiorespiratory arrests associated with severe metabolic acidosis or anemia were more common in children without neurological involvement.

In univariate analysis, several clinical and laboratory features (coma, respiratory distress, a temperature gradient between the periphery and the trunk, delayed capillary refill time, splenomegaly, hepatomegaly, severe anemia, high parasitemia, hypoglycemia, bacteremia, hyperkalemia, thrombocytopenia, and leucocytosis) were associated with increased mortality. Factors independently associated with death were impaired consciousness or coma, hypoglycemia, severe anemia, bacteremia, hyperkalemia, and respiratory distress (TABLE 5). The same risk factors were associated with mortality. Factors independently associated with increased mortality included past history of seizures (AOR, 3.50; 95% CI, 2.78-4.42), fever lasting 2 days or less (AOR, 2.02; 95% CI, 1.64-2.49), delayed capillary refill time (AOR, 3.66; 95% CI, 2.40-5.56), acidosis (AOR, 1.55; 95% CI, 1.29-1.87), and hypoglycemia (AOR, 2.11; 95% CI, 1.31-3.37). An additional diagnosis (comorbidity) and severe anemia were independently associated with the absence of neurological involvement (TABLE 4).

<table>
<thead>
<tr>
<th>Table 3. Admission Characteristics</th>
<th>Neurological Involvement, No./Total (%) of Patients*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>Present 4884/9310 (52.5) Absent 5361/10 246 (52.3)</td>
<td>.85</td>
</tr>
<tr>
<td>Age, median (IQR), mo</td>
<td>Present 26 (15-41) Absent 21 (10-40)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Head circumference, &lt;−2 SD for age†</td>
<td>Present 371/3305 (11.2) Absent 226/1935 (11.7)</td>
<td>.62</td>
</tr>
<tr>
<td>Wasting (weight for height z score &lt;−2)‡</td>
<td>Present 1241/5732 (21.7) Absent 810/4408 (18.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of seizures</td>
<td>Present 1338/3841 (34.8) Absent 349/2371 (14.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Symptoms at admission Fever</td>
<td>Present 6019/6231 (96.6) Absent 4718/4894 (96.4)</td>
<td>.57</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Present 1336/5339 (25.0) Absent 1638/3461 (37.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cough</td>
<td>Present 1996/6230 (32.0) Absent 2144/4893 (43.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Present 530/5585 (9.5) Absent 648/4883 (13.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of illness, median (IQR), d</td>
<td>Present 2 (1-3) Absent 3 (2-3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical signs at admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>Present 102/6042 (1.7) Absent 83/4529 (1.8)</td>
<td>.58</td>
</tr>
<tr>
<td>Delayed capillary refill‡</td>
<td>Present 646/6392 (10.1) Absent 212/4680 (4.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Temperature gradient§</td>
<td>Present 809/3840 (21.1) Absent 351/2371 (14.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Present 4271/9313 (45.9) Absent 6404/10 247 (62.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Present 662/6391 (10.4) Absent 286/4679 (6.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Respiratory distress§</td>
<td>Present 1209/6521 (18.5) Absent 906/5331 (17.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Sustained nasal flaring</td>
<td>Present 528/4884 (10.8) Absent 249/3022 (8.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Deep breathing</td>
<td>Present 760/6520 (11.7) Absent 221/5329 (4.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Subcostal retractions</td>
<td>Present 658/6227 (10.6) Absent 579/4890 (11.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Laboratory results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe anemia</td>
<td>Present 870/9307 (9.3) Absent 2039/9744 (20.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Present 1910/3904 (48.9) Absent 735/2007 (36.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White blood cell count, mean (SD), x10³/µL</td>
<td>Present 13.7 (8.9) Absent 14.7 (10.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parasite density, geometric mean (95% CI), x10³/µL</td>
<td>Present 42.0 (40.0-44.1) Absent 30.4 (29.0-31.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Present 322/3441 (9.3) Absent 70/1457 (4.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Present 1295/3652 (35.5) Absent 929/2859 (32.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Hypoanemia</td>
<td>Present 2249/4094 (54.9) Absent 1026/1922 (53.4)</td>
<td>.26</td>
</tr>
<tr>
<td>Potassium level</td>
<td>Present 70/4088 (1.7) Absent 50/1917 (2.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Present 595/4088 (14.6) Absent 188/1917 (9.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>Present 665/3659 (18.2) Absent 311/1619 (19.2)</td>
<td>.37</td>
</tr>
<tr>
<td>creatinine level &gt;0.90 mg/dL ([&gt;80 µmol/L])</td>
<td>Present 126/5627 (2.2) Absent 122/4151 (2.9)</td>
<td>.02</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>Present 924/9313 (9.9) Absent 1901/10 247 (18.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IQR, interquartile range.

*Unless otherwise indicated.
†The 1978 World Health Organization standards were used.
‡Indicates when refill time is greater than 2 seconds.
§Subjective temperature difference between the trunk and the peripheries.
¶Presence of sustained nasal flaring, deep acidotic breathing, or subcostal retractions.
*Presence of an additional diagnosis when the primary diagnosis is malaria.

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associated with death in the subset of patients with neurological involvement.

**Neurological Deficits at Discharge**

Of 7281 children with neurological involvement, 159 (2.2%) had neurological deficits at discharge. Neurological deficits were observed in 2.1% of survivors with seizures, 4.4% with agitation, 3.6% with prostration, and 6.4% with impaired consciousness or coma. Deficits included motor disorders (spasticity and central hypotonia), ataxia, movement disorders (choreoathetoid, tremors, and dystonic posturing), visual, hearing, and speech impairments, and continuing epileptic seizures. Behavioral problems were reported in 11% of those with neurological deficits and included hyperactivity, violent and impulsive behavior, hallucinations, excessive eating, and fear or anxiety. Presentation with impaired consciousness (AOR, 6.9; 95% CI, 4.6-10.2; \( P < .001 \)) and recurrence of seizures in the hospital (AOR, 2.7; 95% CI, 1.9-4.1; \( P < .001 \)) were independently predictive of neurological deficits at discharge.

**Comment**

Neurological involvement occurred in almost half of the children admitted with acute falciparum malaria and commonly manifested as seizures, prostration, impaired consciousness, or coma. It was associated with increased mortality and neurological sequelae. Although prostration may be a general feature of severe systemic illness, the occurrence of seizures in 60% of patients suggests frequent involvement of the central nervous system.

**Burden of Neurological Involvement in Children With Acute Falciparum Malaria**

In children younger than 5 years, the mean incidence of admission with malaria in this area with less than 1 to 120 infectious mosquito bites a year was 2694 per 100,000 persons and at least 1156 per 100,000 persons were exposed to malaria-related brain insults annually between 1992 and 2004. The risk was lower in children older than 5 years.

In 1998, the midyear for this study, there were an estimated 94.3 million children younger than 5 years and 77.8 million children aged 5 to 9 years living in areas with stable malaria transmission in sub-Saharan Africa. Applying our estimates to these population denominators, at a minimum 2.5 million children younger than 5 years were admitted to hospitals with malaria, of whom 1.1 million had exposure to potential brain injury every year from 1992 to 2004. Similar annual figures for children aged 5 to 9 years are 267,632 and 93,360, respectively. These numbers are an absolute minimum because they do not account for children from the study area who did not attend our hospital. Previous estimates from the study area indicate that two thirds of deaths in children younger than 5 years occur outside the hospital. In addition, the annual entomological inoculation rates in the study area (<1-121 per person) is lower than the overall figures for the continent (0-884 per person). These estimates also do not include areas with unstable (epidemic prone) transmission in Africa. However, 10% of the incidence may be an overestimate due to the inclusion of readmissions in the numerator.

Traditionally, neurological involvement in childhood falciparum malaria has been defined as cerebral malaria, the extreme form of neurological involvement, and has been characterized by seizures and coma. This study shows that emphasis on cerebral malaria alone may be missing other syndromes with the potential to damage the brain. We found that less than 20% of those with neurological illness attributable to malaria fulfilled the definition of cerebral malaria and propose the term *malaria with neurological involvement* to include all of these illnesses. The public health importance of such neurological involvement is enormous. Recent studies described a combination of long-term neurological and cognitive impairments in 24% of children exposed to cerebral malaria or malaria with multiple seizures and an increased risk for epilepsy. In addition, the longer duration of inpatient...
stay and more severe illness may translate into higher health care costs. It is estimated that the cost of treating malaria with cerebral features in a child in district hospitals in sub-Saharan Africa is US $44 to $105 compared with US $33 to $57 for a child without cerebral features.25

**Risk Factors for Neurological Involvement**

Seizures were reported in almost 40% of children admitted with malaria compared with 12% of children with other acute medical illnesses. The proportion of admitted children with neurological involvement (in particular, seizures) increased until 1997. Possible reasons for this include an increasing awareness of the problem, patient selection, and a growing confidence of the community in the ability of the hospital to manage seizures.26 Seizures were associated with high parasitemia but not fever or hyponatremia, supporting the hypothesis that falciparum malaria might be epileptogenic per se.27-30 The presence of additional neurological features supports the hypothesis of direct cerebral involvement. However, it is also likely that some seizures in malaria are simple febrile seizures similar to those seen in nonmalarial endemic areas. It is also notable that not all children with cerebral malaria reported seizures and those without seizures but with coma had a worse outcome, suggesting there are other mechanisms by which coma might develop.

The following factors may contribute to the pathogenesis of neurological involvement in childhood malaria: biochemical perturbations (hypoglycemia, acidosis), impaired perfusion, high parasitemia, and some children may have a predisposition to seizures (higher frequency of history of seizures). Although peripheral parasitemia correlates poorly with vascular sequestration,31,32 high parasite density does predict poor outcome in cerebral malaria.11 This may be due to systemic derangements in immunologic, metabolic, and cardiorespiratory functions. These changes may be associated with altered consciousness32 and may precipitate or lower the threshold for seizures. We propose that neurological involvement in falciparum malaria may arise from (1) a direct effect of sequestered parasites possibly through parasite-induced toxins or immune responses to sequestered parasites on neuronal/blood-brain barrier function or mechanical vascular blockage or (2) an indirect effect from parasite-induced local and systemic metabolic derangements or impaired perfusion (impaired delivery of substrates). Genetic susceptibility to seizures,33 including febrile seizures, may be important. Acute and long-term imaging studies, especially magnetic resonance imaging, will greatly assist in determining pathogenesis.

**Outcome of Malaria With Neurological Involvement**

Overall, involvement of the central nervous system was associated with increased mortality and neurological sequelae in survivors. The risk of death and neurological damage increased with lower levels of consciousness at admission (Table 2). The proportion of children admitted with metabolic acidosis or hypoglycemia also increased with worsening level of consciousness and rising mortality. Children with single seizures without additional neurological features had low mortality (minimal risk) but the presence of prostration, impaired consciousness, or secondary deterioration in consciousness was associated with increased mortality (high risk). Identification and supportive treatment may improve outcome in these patients.34

Two percent of the patients with neurological involvement, and in particular those with impaired consciousness or repeated seizures, had gross neurological deficits at discharge similar to those previously described.32 At least one tenth of those with deficits had behavioral problems. Future studies should characterize these behavioral disorders and suggest interventional measures.

Apart from the difficulties in ascertaining readmissions, this study has limitations due to its reliance on retrospective data from 1 hospital based only on inpatients, possible incomplete parental reporting, and the possibility that some children in the study area could have received care from other health units. These have the consequence of underreporting the extent of the burden of malaria and its sequelae. Our data also do not allow analysis of any contribution of human immunodeficiency virus infection to neurological involvement. This is an important area that needs further study.

**CONCLUSION**

Neurological involvement is common in children admitted with acute falciparum malaria and goes beyond what has been traditionally regarded as cerebral malaria. It is associated with a history of seizures in previous illnesses, impaired perfusion, perturbations in biochemical functions, high parasitemia, mortality, and neurological deficits. The high frequency of neurological involvement suggests that many children in sub-Saharan Africa are exposed annually to malaria-related brain insults.

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