Neurologic outcomes in retinopathy-negative cerebral malaria survivors

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ABSTRACT

Objectives: Patients surviving retinopathy-positive cerebral malaria (CM) are at high risk for the development of epilepsy, developmental disabilities, and behavioral abnormalities. We aimed to establish whether retinopathy-negative CM is also a risk factor for these outcomes.

Methods: Between 2005 and 2007, survivors of CM and concurrently hospitalized controls in Blantyre, Malawi, were followed to assess the development of neurologic abnormalities. At discharge and every 3 months thereafter, incident cases of epilepsy and developmental disabilities were ascertained using screening questionnaires and confirmatory neurologic examinations. Incident cases of epilepsy and developmental disabilities were compared in retinopathy-negative CM survivors to controls and retinopathy-positive CM survivors.

Results: Thirty-five retinopathy-negative CM survivors were enrolled. Their neurologic outcomes were compared to 132 retinopathy-positive CM survivors and 272 controls. Compared to survivors of retinopathy-positive CM, children without malaria retinopathy have an equal odds of adverse neurologic outcome (odds ratio [OR] = 1.0, 95% confidence interval [CI] 0.4–2.2). Eleven of 35 survivors of retinopathy-negative CM had at least 1 adverse neurologic outcome compared to 2 of 272 controls (OR 61.9, 95% CI 13.0–295.5). In retinopathy-negative CM survivors, a Blantyre Coma Scale score ≤1 on admission was associated with an adverse outcome.

Conclusions: Compared with controls, children surviving either retinopathy-negative or -positive CM are at similar high risk for adverse neurologic outcomes. Studies to evaluate preventive and therapeutic strategies in children with both retinopathy-negative and -positive CM are needed to improve mortality, morbidity, or both.

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GLOSSARY

CI = confidence interval; CM = cerebral malaria; OR = odds ratio.

Cerebral malaria (CM) is defined as an otherwise unexplained coma in a patient with circulating Plasmodium falciparum parasitemia.1 Children with CM are not a homogeneous group. A clinical-autopsy study revealed that approximately 23% of children meeting case criteria for CM lacked evidence of sequestration of parasitized red blood cells in cerebral vasculature.2 This pathologic finding is thought to indicate that P falciparum was most likely responsible for the patient’s illness and coma. Premorbid differentiation of children with case-defined CM but without cerebral sequestration was impossible until the description of malaria retinopathy and correlation of retinopathy status with autopsy findings. The presence of malaria retinopathy is 95% sensitive and 90% specific for the histologic presence of sequestered parasitized erythrocytes and suggests that the clinical syndrome in an individual patient is likely caused by P falciparum.3

Retinopathy-negative CM may represent an asymptomatic incidental parasitemia with a second exposure (possibly viral) producing fever and coma.4 A clinical-autopsy study supported
this hypothesis, finding other infectious and noninfectious causes of coma in patients dying of retinopathy-negative CM.

To evaluate whether retinopathy-negative CM is a risk factor for the development of epilepsy or neurodisabilities, we evaluated neurologic outcomes in children with retinopathy-negative CM who were included in a prospective cohort of CM survivors. The outcomes of the 35 patients with retinopathy-negative CM who were enrolled in the parent study and followed to study completion have not previously been described and are the subject of this analysis.

METHODS Details of the methods used during this study have been previously published. Briefly, we performed a prospective cohort study of CM survivors and concurrently admitted controls. Patients with CM fulfilled WHO case criteria for this condition. From the commencement of our study in 2005, children were administered a topical mydriatic shortly after admission and a trained ophthalmologist and expert in malaria retinopathy used direct ophthalmoscopy to examine all CM cases to determine retinopathy status. Retinopathy-negative cases were enrolled only between May 2005 and May 2007. When the importance of malaria retinopathy became clear, subjects enrolled after May 2007 were limited to those who were retinopathy-positive.

Cases and controls were admitted primarily during the malaria season, which in Malawi occurs between the months of January and June each year. In 2005 only, enrollment was continued into the dry season, July through December. All children were admitted to Queen Elizabeth Central Hospital, a tertiary referral center located in Blantyre, Malawi. Children who fulfilled case criteria for CM (an otherwise unexplained coma in a patient with asexual forms of \( P \) falciparum on peripheral blood smear) were admitted to the Pediatric Research Ward, a section of the hospital specially suited to the higher level of nursing care required for comatose patients. Control patients were the first eligible, consenting child admitted to the General Pediatric Ward after the CM case was enrolled. Controls were age-matched to within 6 months of CM cases. Inclusion criteria for controls were a normal level of consciousness and no history of unprovoked seizures before admission.

At study enrollment, the Ten Questions Screen was administered to the parent or guardian accompanying each patient. This questionnaire screens for the presence of neurodevelopmental disabilities. It has been validated in similar geographic and economic contexts for children as young as 2 years old, and shows good (85%) sensitivity in the detection of moderate to severe disabilities in children older than 2 years. Children without developmental abnormalities may screen positive on the Ten Questions Screen due to a history of febrile seizure. Therefore, in children who screened positive, a parent or guardian was questioned further to confirm the presence of neurodisabilities. The families of all children were also administered the Epilepsy Screening Questionnaire. This tool has been shown to be 79% sensitive and 93% specific in the detection of epilepsy. Children with preexisting unprovoked seizures were excluded from the study. Those who screened positive on the Ten Questions and were found to have preexisting neurodisabilities were enrolled but evaluated only for the development of epilepsy and behavioral disorders.

Hospital protocols followed with our cohort have been previously described. At hospital discharge a neurologic examination was performed by the attending clinician. After discharge children were seen by a study nurse every 3 months until study completion. At these follow-up visits, families were administered the Ten Questions Screen and the Epilepsy Screening Questionnaire to ascertain incident cases of neurodisabilities or epilepsy. All children who were screened as abnormal at hospital discharge or failed a postdischarge screen were examined by a neurologist (G.B.) to confirm the diagnosis and characterize the neurodisability or seizure type. Children who at hospital admission screened negative on the Ten Questions screen and were later found to have new onset developmental abnormalities (motor, sensory, or language) on neurologic examination were diagnosed as having new neurodisabilities. Children who at hospital admission screened negative on the Epilepsy Screening Questionnaire and later had 2 or more unprovoked seizures were diagnosed as having new-onset epilepsy. After hospital discharge, some parents reported that their children had developed new behavioral problems. These were evaluated and described by the neurologist.

Enrollment closed in June 2007 and assessments for the development of neurodisabilities and epilepsy continued until December 2009, allowing at least an 18-month follow-up period for all patients.

Statistical analysis. Admission characteristics of retinopathy-positive CM, retinopathy-negative CM, and controls were compared with analysis of variance; results have been previously reported. This analysis consisted of an unmatched comparison of retinopathy-negative CM survivors with controls and retinopathy-positive CM survivors. The preadmission characteristics of retinopathy-negative vs retinopathy-positive CM survivors were compared and odds ratios (OR) (with 95% confidence intervals [CI]) for the development of epilepsy, neurodisabilities, disruptive behavioral disorder, or any adverse neurologic outcome were compared between retinopathy-negative CM survivors, retinopathy-positive CM survivors, and controls. Risk factors for any adverse neurologic outcome or death in retinopathy-negative CM survivors were sought by determining the association between clinical and laboratory characteristics at hospital admission (age, gender, body mass index, first-degree family member with epilepsy, Blantyre Coma Scale score less than 2 on admission, hemocrit on admission, lactate greater than 5 mmol/L on admission, hypoglycemia [defined as a glucose less than 2.2 mmol/L], seizure during the acute illness, and time to coma resolution in hours) with adverse neurologic outcomes using \( t \) tests or odds ratios with 95% confidence intervals. For \( t \) test comparisons, population variance was assessed and if a statistically significant (\( p < 0.05 \)) difference in population variances was found, nonparametric (Kruskal-Wallis) tests were performed.

Separate logistic regression analyses were performed for each of the adverse neurologic outcomes: developmental abnormalities, epilepsy, or disruptive behavioral disorder. The covariates assessed included gender, Blantyre Coma Scale score less than or equal to 1 on admission, maximum temperature, length of time...
of coma resolution, and acute seizures during hospital admission. These covariates were selected because they influence the odds of an adverse neurologic outcome in retinopathy-positive CM survivors.1 We additionally controlled for known risk factors for adverse neurodevelopmental outcomes or the development of epilepsy including male gender, a personal history of provoked seizures, or having a first-degree family member with epilepsy.

RESULTS Thirty-five children with retinopathy-negative CM were enrolled. These children were compared to 132 retinopathy-positive CM survivors and 272 controls. As previously reported, the 3 comparison groups did not significantly differ in terms of age, gender, birthweight, admission temperature, body mass index, history of perinatal problems, or history of severe malaria before the index admission.10

One of the 35 children with retinopathy-negative CM was found to have a neurodevelopmental disability on enrollment screening and confirmatory parental questioning. The control group had a higher proportion of preadmission neurodisabilities (17/272 or 6.3%) than either the retinopathy-negative CM (1/35 or 2.9%) or retinopathy-positive CM (5/132 or 3.8%) groups, but the difference was not statistically significant (p = 0.10). Five of the children with retinopathy-negative CM had a first-degree family member (3 had a parent and 2 an older sibling) with epilepsy. The odds that a child diagnosed with retinopathy-negative CM had a first-degree family member with epilepsy compared to a control patient were significant (OR = 3.61, 95% CI = 1.19–10.95).

Of the 35 children with retinopathy-negative CM enrolled, 20 (57.1%) completed the study, defined as either development of an adverse outcome or attendance at follow-up examinations until December 2009. Completion rates were significantly lower compared to the retinopathy-positive and control groups (77% and 65%, respectively, p = 0.008).5 Neither a child’s age nor gender was associated with loss to follow-up. The duration of follow-up from recruitment to either an adverse outcome or attrition for the retinopathy-negative group was a mean of 418 days (SD 322), which did not differ significantly from the retinopathy-positive (mean 534 days, SD 453 days, p = 0.15)5 or control groups (mean 446 days, SD 374 days, p = 0.67).5 In all 3 comparison groups, children enrolled later in the study period or those who developed new neurodisabilities were more likely to follow up until study completion than those enrolled earlier or who were normal at their last study visit.

At follow-up, some parents spontaneously reported behavioral abnormalities in their children. Neurologic evaluation revealed children with impulsivity, hyperactivity, aggression, and inattentiveness. We termed this disruptive behavioral disorder, as diagnostic criteria for attention-deficit/hyperactivity disorder have not been validated in Malawian children. Although not a primary outcome measured in the parent study, the number of children who developed these behaviors was collected and analyzed.

During the follow-up period, children surviving retinopathy-negative CM were at increased risk of developing epilepsy, new neurodisabilities, and disruptive behavioral disorders compared to controls (table). Children who survived retinopathy-negative CM were equally likely to develop adverse neurologic outcomes as were children surviving retinopathy-positive CM. Overall, 11 (31.4%) retinopathy-negative CM survivors developed at least 1 adverse neurologic event during follow-up. On univariate analysis, none of the risk factors identified as associated with the development of adverse outcomes in patients with retinopathy-positive CM were found to be risk factors for adverse outcomes in retinopathy-negative CM survivors. For children with retinopathy-negative CM there were no statistically significant differences between those who developed adverse outcomes and those who did not.

Logistic regression analysis revealed that when all other covariates for adverse neurologic outcomes in

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Retinopathy-negative CM survivors</th>
<th>Retinopathy-positive CM survivors</th>
<th>Controls</th>
<th>OR (95% CI) comparing retinopathy-negative survivors with controls</th>
<th>OR (95% CI) comparing retinopathy-negative CM survivors with retinopathy-positive CM survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>6/35 (17.1)</td>
<td>12/132 (9)</td>
<td>0/272 (0)</td>
<td>Undefined</td>
<td>2.1 (0.7–6.0)</td>
</tr>
<tr>
<td>New neurodisabilities</td>
<td>7/34 (20.6)</td>
<td>28/131 (21.4)</td>
<td>1/272 (0.4)</td>
<td>70.3 (8.3–592.6)</td>
<td>0.9 (0.3–2.2)</td>
</tr>
<tr>
<td>Disruptive behavioral disorder</td>
<td>3/35 (8.6)</td>
<td>14/132 (10.6)</td>
<td>1/272 (0.4)</td>
<td>25.4 (2.6–251.6)</td>
<td>0.8 (0.2–2.9)</td>
</tr>
<tr>
<td>Any adverse neurologic outcome</td>
<td>11/35 (31.4)</td>
<td>42/132 (32)</td>
<td>2/272 (0.7)</td>
<td>61.9 (13.0–295.5)</td>
<td>1.0 (0.4–2.2)</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; CM = cerebral malaria; OR = odds ratio.

a Outcomes are not mutually exclusive. Data are n/N (%) or OR (95% CI).

b Excludes children with a neurodisability at enrollment.
retinopathy-positive CM survivors were included, only a Blantyre Coma Scale score \( \leq 1 \) on admission was associated with an adverse outcome in patients with retinopathy-negative CM. Children with a coma score greater than 1 on admission were at lower odds of developing epilepsy (OR = 0.177, Wald 95% CI = 0.033–0.943) and had a trend toward a decreased risk of the development of neurodisabilities (OR = 0.241, Wald 95% CI = 0.057–1.021).

**DISCUSSION** This prospective study of retinopathy-negative CM survivors shows that long-term neurologic sequelae are frequent in this condition. The odds of any abnormal neurologic outcome are similar (61.9 vs 63.0, respectively) for retinopathy-negative and retinopathy-positive CM survivors compared to unexposed controls.

In children surviving retinopathy-positive CM, known risk factors for the development of epilepsy are a higher maximum temperature and seizures during admission. Male gender is a risk factor for the development of neurodisabilities and higher temperature or a deeper coma (Blantyre Coma Scale score \( \leq 1 \)) upon admission are risk factors development of disruptive behavioral disorder. In contrast, in children surviving retinopathy-negative CM, only a deeper coma upon admission was associated with the development of epilepsy. No other clear risk factors for the development of adverse neurologic outcomes could be discerned in this group, possibly due to smaller sample size or the heterogeneity of etiologies for these children’s illnesses. Although these findings must be considered preliminary, the lack of concordance between risk factors for adverse neurologic outcomes in retinopathy-positive vs retinopathy-negative CM survivors supports the hypothesis that these disorders have differing underlying pathophysiologies. Importantly, the number of covariates assessed by logistic regression may have been too many for our small sample size. Therefore, the finding that a Blantyre Coma Scale score \( \leq 1 \) was associated with an adverse neurologic outcome in retinopathy-negative CM survivors must be considered preliminary.

Children with retinopathy-negative CM had a higher odds of having a first-degree family member with epilepsy compared to unexposed controls, suggesting that they may have a genetically lowered seizure threshold, predisposing them to develop seizures during any severe medical illness. It is possible that some children diagnosed with retinopathy-negative CM may have a prolonged postictal state, incidental parasitemia, and a second nonmalarial co-infection. When exposed to an identical infectious challenge, children with no family history of epilepsy may be less likely to seize, less likely to have a postictal state, and thus less likely to be diagnosed with CM. Further studies to explore this possibility are warranted.

Limitations of our study are that we followed fewer cases of retinopathy-negative CM survivors compared to children with retinopathy and that follow-up for the retinopathy-negative patients was significantly shorter than for either controls or those with retinopathy-positive CM. Our patient group was evaluated using the Epilepsy Screening Questionnaire and the Ten Questions Screen. The former has not been validated in Malawian children and the latter lacks sensitivity in children younger than 2 years of age or for the detection of mild neurodisabilities. As the 3 patient groups were matched on age, approximately 20% of each group was less than 2 years old at study enrollment.

Surviving either retinopathy-negative or retinopathy-positive CM is a risk factor for the development of epilepsy, neurodisabilities, and disruptive behavioral disorders. Our analysis highlights the importance of CM as the cause of a large number of childhood neurologic abnormalities. If there are 575,000 cases of WHO case defined CM annually (a possibly low estimate) with a 15% mortality and 30% neurologic morbidity in survivors, then approximately 150,000 new cases of neurodisabilities, epilepsy, and behavioral disorders are caused by CM each year. Studies to evaluate preventive and therapeutic strategies in children with retinopathy-negative and retinopathy-positive CM are needed to improve mortality, morbidity, or both.

**AUTHOR CONTRIBUTIONS**

Douglas Postels drafted and revised the manuscript for intellectual content. Terrie Taylor conceptualized the study and revised the manuscript for intellectual content. Malcolm Molyneux conceptualized the study and revised the manuscript for intellectual content. Kara Mannor analyzed and interpreted the data. Peter W. Kaplan conceptualized the study and revised the manuscript for intellectual content. Konwdani Kawaza revised the manuscript for intellectual content. Greschen Birbeck designed the study and revised the manuscript for intellectual content. Douglas Postels and Kara Mannor completed the statistical analysis.

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**DISCLOSURE**

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