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Cerebral Malaria in Children Is Associated With Long-term Cognitive Impairment

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Abstract

OBJECTIVE—Cerebral malaria affects >785 000 African children every year. We previously documented an increased frequency of cognitive impairment in children with cerebral malaria 6 months after their initial malaria episode. This study was conducted to determine the long-term effects of cerebral malaria on the cognitive function of these children.

METHODS—Children who were 5 to 12 years of age and presented to Mulago Hospital, Kampala, Uganda, with cerebral malaria (n = 44) or uncomplicated malaria (n = 54), along with healthy, asymptomatic community children (n = 89), were enrolled in a prospective cohort study of cognition. Cognitive testing was performed at enrollment and 2 years later. The primary outcome was presence of a deficit in ≥1 of 3 cognitive areas tested.

RESULTS—At 2-year follow-up testing, 26.3% of children with cerebral malaria and 12.5% with uncomplicated malaria had cognitive deficits in ≥1 area, as compared with 7.6% of community children. Deficits in children with cerebral malaria were primarily in the area of attention (cerebral malaria, 18.4%, vs community children, 2.5%). After adjustment for age, gender, nutrition, home environment, and school level, children with cerebral malaria had a 3.67-fold increased risk for a cognitive deficit compared with community children. Cognitive impairment at 2-year follow-up was associated with hyporeflexia on admission and neurologic deficits 3 months after discharge.

CONCLUSIONS—Cerebral malaria is associated with long-term cognitive impairments in 1 of 4 child survivors. Future studies should investigate the mechanisms involved so as to develop interventions aimed at prevention and rehabilitation.

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Keywords

cerebral malaria; cognitive; deficit; impairment; *P falciparum*

What's Known on This Subject

Retrospective studies have suggested that cerebral malaria in children is associated with long-term cognitive deficits.

What This Study Adds

This is the first prospective study to document long-term cognitive impairment in children with cerebral malaria. We document that deficits found early persist long-term, whereas additional new deficits are discovered on long-term follow-up.

Cerebral Malaria (CM), which is estimated to affect 785 000 children who are younger than 9 years in sub-Saharan Africa every year,[1] is among the deadliest forms of malaria, with an average mortality rate estimated at 18.6%.[2] Gross neurologic deficits are frequent at the time of discharge but generally resolve within 6 months of discharge.[3] A number of retrospective studies have suggested that CM is associated with higher frequencies of more subtle cognitive deficits as long as 3 to 9 years after the episode of CM,[4-8] but, to date, no long-term prospective studies of cognitive impairment after CM have been performed. In retrospective studies, the effects of variables such as home environment or nutrition, which may be important in cognitive development and which may change over time, cannot be assessed in control children at the same age and time as the CM episode occurred in the case children with CM. In addition, changes in cognitive function over time cannot be assessed in such studies.

We recently demonstrated, in a prospective study, that 6 months after an episode of CM, children with CM have a significantly increased frequency of cognitive deficits as compared with community children (CC).[9] Children with uncomplicated malaria (UM) also had an increased frequency of cognitive deficits as compared with CC, but this difference was not statistically significant. To assess the long-term effects of CM and UM, we performed follow-up cognitive testing of children in this cohort study 2 years after enrollment.

METHODS

Study Population and Recruitment

The study was conducted at Mulago Hospital, Kampala, Uganda, from November 2003 to July 2006. Full details of this study cohort, including enrollment criteria and the baseline demographic, clinical, and laboratory findings, were published previously in a study that documented cognitive outcomes of the cohort children at enrollment and 3 and 6 months later.[9] Briefly, children 5 to 12 years of age were enrolled in the study. The mean age of children who are admitted with a diagnosis of CM to Mulago Hospital is 3.2 years (unpublished data), but the cognitive tests used in this study (see Cognitive Testing below) are reliable only in children who are older than 5 years, so only children who were older than 5 years were included in this study. Children with CM were enrolled when they were admitted to Mulago Hospital and met the World Health Organization criteria for CM: coma (Blantyre coma scale ≤ 2 or Glasgow coma scale ≤ 8), *Plasmodium falciparum* on blood smear, and no other known cause for coma. Lumbar punctures were performed to assess for meningitis and encephalitis. Children with UM were enrolled from the hospital's pediatric emergency care clinic or an outpatient malaria clinic at the hospital. Children were considered to have UM when they had signs and

symptoms of malaria (fever, chills, vomiting, headache), *P falciparum* infection on blood smear, and no evidence of World Health Organization criteria for severe malaria (CM, severe malarial anemia, respiratory distress, shock, spontaneous bleeding, hypoglycemia, repeated seizures, hemoglobinuria, hypoglycemia, prostration, impaired consciousness, jaundice, or hyperparasitemia) or other acute illness. CC were recruited from the extended family or neighborhood of children with CM or UM. CC and children with UM were recruited to be in the same age range (5–12 years) as children with CM. A history and physical examination was performed to ascertain that the CC were healthy at the time of enrollment. Exclusion criteria at enrollment for all 3 groups included (1) a history of meningitis, encephalitis, or any brain disorder, including CM or repeated seizures, (2) a history of developmental delay, (3) previous admission for malnutrition, (4) a history of chronic illness, and (5) failure to show up at the appointment for cognitive testing. In addition, children who were recruited for the CC cohort were excluded when they had evidence of acute illness on physical examination, had been treated for an acute illness in the past month, or had admitted for malaria in the past 6 months. All CC were tested for asymptomatic *P falciparum* infection by microscopy of peripheral blood smears; 21 (24.4%) of the 86 children enrolled were infected and were treated with chloroquine and sulfadoxine/pyrimethamine, which was the national guideline for treatment of UM at the time of the study.[10] These children were not excluded from the study.

A total of 217 children were initially recruited for the cognitive study (51 children with CM, 70 children with UM, and 97 CC). Of these children, 187 children (44 children with CM, 54 children with UM, and 89 CC) were enrolled and completed initial cognitive testing (Fig 1). Five children with CM were excluded because of misdiagnosis (meningitis [1], rabies [1], and coma score not correctly calculated [1]) or previous severe illness (2), and 2 died during the admission. Fourteen children who had UM and were recruited at the time of diagnosis and treatment did not return for cognitive testing 72 hours after treatment, and 2 were excluded for other concurrent illness. Eight CC were excluded because of a previous severe illness (6), history of coma (1), or incorrect initial calculation of age (1). Cognitive testing was performed at discharge for children with CM, 3 days after treatment for UM for children with UM, and at the time of enrollment for CC. Testing was also performed at 6-month follow-up as previously reported.[9] Approximately 24 months after initial enrollment, parents or guardians of children in the study cohort were contacted and asked to participate in a follow-up study in which their children would again receive follow-up examination and cognitive testing. Of the 187 children originally tested, 165 were followed up for cognitive testing 24 months after enrollment (Fig 1).

Written informed consent was obtained from the parents or guardians of study participants. Ethical approval for the study was granted by the institutional review boards for human studies at Makerere University Faculty of Medicine, University of Minnesota, and University Hospitals of Cleveland and Case Western Reserve University. The original cohort was enrolled while the principal investigator (Dr John) was a faculty member at Case Western Reserve University.

Clinical and Demographic Assessment

All study participants had a complete medical history and physical examination. Detailed medical history findings and physical findings, including specific neurologic findings, were recorded for children with CM. Nutrition was assessed by comparing weight for age with published norms and obtaining a standardized *z* score (Epi Info 6 [Centers for Disease Control and Prevention, Atlanta, GA]). Socioeconomic status was assessed using a scoring instrument developed by the study team for this area that incorporated a checklist of material possessions, quality of home environment and home structure, living density, food resources, cooking and bathroom facilities, and access to electricity and clean water. Home environment was assessed

using a version of the Home Observation for Measurement of the Environment (HOME) inventory[11] adapted for Uganda. The HOME inventory as modified is a 58-question assessment of the stimulation and learning opportunities offered by the child's home environment. Level of education of the child and mother were scored as follows: none, 0; nursery, 1; primary school grades 1 to 7, 2 to 8; secondary education, 9; and postsecondary school, 10. A simple assessment of potential developmental delay before enrollment was performed by asking the parents or guardians of the enrolled children whether the child was slower than other children his or her age in terms of his or her skills in walking, talking, or playing with other children. Interim history, including history of reported seizures, episodes of febrile illness, and hospitalizations between 6 and 24 month testing, was obtained and a physical examination was performed at 24-month testing.

Cognitive Testing

Neurocognitive assessments that were previously tested in children from other sub-Saharan African countries were used in this study. Instructions and verbal items for all tests were translated into and back-translated from Luganda (the most spoken local language) and pilot tested with 30 healthy school children (aged 5–12 years). Neurocognitive assessments focused on cognitive ability and memory (the Kaufman Assessment Battery for Children), attention (the visual form of the computerized Test of Variables of Attention), and tactile-kinesthetic learning (the Tactual Performance Test). Complete details of this study testing, including specific details of areas and methods of testing, have been previously reported.[9] Primary outcome measures that were used to define cognitive deficits were summary variables that assessed working memory (sequential processing of the Kaufman Assessment Battery for Children), executive attention (signal detection D prime test of the Test of Variables of Attention), and tactile-based learning (total time per block of the Tactual Performance Test).

Statistical Analysis

To account for the influence that age has on the neurocognitive assessments, we converted each raw outcome into an age-specific standardized (*z*) score, based on the scores of CC for each year of age. Eleven- and 12-year-olds were grouped together because of the small number of children of these ages. Although age distribution of the 3 groups was similar (Table 1), the assessment of *z* scores requires age-specific scoring because even among healthy children, younger children will have lower scores than older children, and *z* scoring using all children results in the lowest *z* scores' clustering in the youngest age group. When appropriate, data were logarithmically (base e) transformed to approximate normality before calculating *z* scores.

A cognitive deficit was defined as a *z* score of less than −2 for working memory and attention and a *z* score of >2 for tactile-based learning. The primary outcome variable, presence of a cognitive deficit in ≥1 of the summary variables 24 months after initial assessment, was decided before data analysis. Because there was no way to generate an overall cognitive score from the primary data of scores in individual areas, the use of cognitive deficit in ≥1 area, which has been used in previous studies of CM or impaired consciousness and cognition,[7,12] was chosen as the best summary assessment of cognitive impairment. Frequencies of cognitive deficits in children with CM and UM were compared with those in CC by χ^2 or Fisher's exact test, as appropriate. The proportions of cognitive deficits among children with CM and UM were also compared with those in CC by using generalized estimating equations with a binomial distribution and a logit link to obtain adjusted odds ratios (ORs).[13] The Statistical Analysis System 9.1 GENMOD procedure was used for OR analyses (SAS Institute, Inc, Cary, NC). This method allows for the possible correlation between children with malaria and CC from the same family. Mean difference in adjusted *z* scores in the areas of attention, working memory, and tactile-based learning was assessed using multiple linear regression. Generalized estimating equations and multiple linear regression estimates were adjusted for age (by use of

the age-specific *z* score), child's school level, gender, nutrition (weight for age), and home environment score. Socioeconomic status and maternal education did not contribute significantly to the models and were not adjusted for in the final models. *P* values reported are for 2-tailed tests. There were a limited number of comparisons between groups, and all secondary outcomes were also defined before analysis, so *P* values were not corrected for multiple comparisons.

Sample-size calculations were done for the original 6-month end point. A sample size of 45 children with CM and 90 CC was calculated to have 80% power to detect a frequency of 20% cognitive deficits in children with CM at 6 months versus a 3% frequency in CC ($\alpha = .05$). With an estimated 10% loss to follow-up, a sample size of 41 children with CM and 81 CC was calculated to have 76% power to detect the same differences in cognitive deficit frequencies at 24 months.

RESULTS

Baseline Characteristics of Children With CM and UM and CC

Baseline characteristics of children with CM and UM and CC were previously reported.[13] Children with CM were more frequently male than were CC (66% vs 50%; $P = .07$), but children with CM and UM and CC did not differ significantly in age, weight, nutritional status, education level, maternal or paternal education level, socioeconomic status, or home environment score (Table 1, as previously reported). Parasite density in children with CM and UM was similar (median [interquartile range]) for CM (32 040 [143 120] and UM (30 320 [88 720]; $P = .65$), whereas in the CC who were parasitemic, parasite density was much lower (median level [interquartile range]: 4960 [7290]; $P < .0001$, compared with CM or UM). Frequency of previous potential developmental delay, as assessed by being "slower than other children their age" in ≥1 of the areas of walking, talking, or playing with others, did not differ significantly between children with CM (3 of 44 [6.8%]) and UM (0 of 54 [0%]) and CC (6 of 89 [6.7%]). Follow-up and testing of children with CM and UM and CC is outlined in Fig 1. Thirty-eight (86.3%) of 44 children with CM, 48 (88.9%) of 54 children with UM, and 79 (88.7%) of 89 CC were tested at 24-month follow-up.

Cognitive and Neurologic Impairment 24 Months After Enrollment

Children with CM had a significantly higher frequency of deficits in ≥1 area of cognition (10 of 38 [26.3%]) than CC (6 of 79 [7.6%]; $P = .006$; Table 1). Deficits were more frequent in CM than CC primarily in the area of attention (7 of 38 [18.5%] vs 2 of 79 [2.5%]; $P = .005$; Table 2). Six of the 7 children who had CM and had cognitive impairment at 6 months had persistent impairment at 24 months, and 4 additional children demonstrated impairment at 24 months that was not present at 6 months. Children with UM had similar frequencies of deficits to CC in ≥1 area of cognition and in each area of cognition (Table 2). After adjustment for age, gender, nutrition, home environment, and child's education level, children with CM had 3.67-fold increased risk for a cognitive deficit as compared with CC (95% confidence interval [CI]: 1.11–12.07; $P = .03$). Additional adjustment for the presence of previous potential developmental delay did not affect the risk for subsequent impairment associated with CM (OR: 3.67 [95% CI: 1.10–12.13]; $P = .03$). Adjusted risk for cognitive deficit did not differ significantly between children with UM and CC (OR: 1.80 [95% CI: 0.51–6.31]; $P = .36$).

Cognitive Outcome Scores Over Time

After adjustment for age, gender, home environment score, nutrition, and child's education level, children with CM had worse *z* scores in all 3 areas of cognition than CC at enrollment, and adjusted scores remained worse in the areas of attention and working memory at 6 months, although these differences were not significant (Table 3). At 24-month follow-up, children

with CM had significantly worse adjusted *z* scores than CC in the area of attention, and the difference in adjusted *z* scores was more pronounced than at 6 months. In contrast, *z* scores in working memory or tactile-based learning at 24-month follow-up were not significantly different between children with CM and CC (Table 3). Children with UM did not have significantly different adjusted *z* scores in any area of cognition as compared with CC at enrollment or 6- or 24-month follow-up (Table 4).

Clinical Factors and Cognitive Deficits in Children With CM

Clinical factors compared in children with CM with and without cognitive deficits included antimalarial use before admission, number of seizures before admission, type of seizure, previous seizure history, temperature, blood pressure, presence of malnutrition, oxygen saturation, deep respirations, decorticate or decerebrate posturing, presence of deep tendon reflexes, dehydration, papillary dilation and reactivity, total duration of coma, duration of coma after quinine treatment, presence and number of seizures after admission, focal neurologic findings, and neurologic deficits at the time of discharge. In addition, laboratory tests compared with cognitive outcome included admission peripheral blood parasite density; total leukocyte, platelet, granulocyte, lymphocyte, and monocyte counts; levels of hemoglobin, glucose, sodium, bilirubin, and creatinine; and presence of stool helminth infection. Finally, a number of interim factors between admission and testing were assessed, including neurologic sequelae, presence of seizures, hospitalization, treatment for malaria, and number of episodes of malaria. Of all of these factors, only diminished deep tendon reflexes on admission and the presence of neurologic sequelae at 3 months were associated with cognitive deficits. Among the 33 children who had CM and had documentation of deep tendon reflexes on admission, 9 (100%) of 9 children with cognitive deficits had diminished reflexes versus 14 (58.3%) of 24 children without deficits ($P = .03$). Three (30%) of 10 children with deficits had neurologic sequelae at 3 months, as compared with 1 (3.6%) of 28 children without deficits ($P = .05$). Duration of coma and number of seizures before admission, which were associated with cognitive deficits at 6 months,[9] were not significantly greater in children with cognitive deficits than in children without deficits at 24 months (mean [SD]: 40.9 [46.1] vs 28.9 [21.4; $P = .15$] and 4.3 [2.6] vs 3.3 [2.8; $P = .22$], respectively). Of note, frequency of seizures, number of seizure episodes, number of febrile episodes, and number of hospitalizations did not differ significantly between groups in the period between 6- and 24-month testing and were not associated with cognitive impairment in children with CM (data not shown).

DISCUSSION

We previously documented in a prospective study that 21.4% of children who were 5 to 12 years of age and had CM had cognitive deficits 6 months after their CM episode, as compared with 5.7% of CC.[9] In the same cohort of children, we now document that 2 years after the episode, cognitive impairment was present in 26.3% of children with CM as compared with 7.6% of CC ($P = .006$). After adjustment for several other potential risk factors, children with CM had a 3.67-fold increased risk for cognitive impairment at 2-year follow-up as compared with CC (95% CI: 1.11–12.07; $P = .03$). This study is the first prospective study to document long-term cognitive impairment in children with CM and confirms the findings of previous retrospective studies that suggested that CM was associated with cognitive injury. If similar frequencies of cognitive deficits occur across the age spectrum of children affected with CM, then >200 000 children annually may sustain cognitive impairment after CM, making CM a major contributor to cognitive impairment in children in sub-Saharan Africa.

Children with CM had worse age-adjusted *z* scores in all 3 areas of cognitive testing at enrollment, a result that could be attributed to their acute illness (Table 3). At 6 months, children with CM still had worse adjusted *z* scores in the areas of attention and working memory than

CC, but the differences no longer achieved statistical significance; however, at 24 months, children with CM again had significantly worse adjusted *z* scores in the area of attention as compared with CC, and the mean difference in adjusted *z* scores between children with CM and CC was even larger than at enrollment. The frequency of cognitive deficits in ≥1 area in children with CM was similar at 6 and 24 months. The finding that only 1 of 7 children with deficits at 6 months did not have a deficit at 24 months suggests that cognitive deficits are not transient. The finding of 4 additional children with deficits at 24 months suggests that clear-cut cognitive impairment may continue to unfold developmentally in the years after the CM episode. The consistency of our findings of risk for cognitive impairment in children with CM as compared with CC at 6 months (adjusted OR: 3.71 [95% CI: 1.29–10.67]; $P = .02$)[9] and 24 months (adjusted OR: 3.67 [95% CI: 1.11–12.07]; $P = .03$) supports the association of CM with cognitive impairment.

The pathogenesis of CM in humans is still incompletely characterized, but it is currently thought that CM results from a number of events, including parasite sequestration that leads to local ischemia and hypoxia; accumulation of $CD4^+$ and $CD8^+$ T cells, monocytes, and platelets; local cytokine release; and stimulation of other pathways, including the kynurenine pathway.[14] Animal models[15,16] and human studies,[17,18] including data from cerebrospinal fluid testing of children in this cohort,[19] suggest a role for microglial activation and central nervous system cytokine production. Any of these factors could lead to neuronal damage or death, which may manifest clinically as long-term cognitive injury as neural networks that support such foundational cognitive skills as attention and working memory continue to differentiate and develop. Animal studies also provide evidence that CM leads to neuronal apoptosis,[20-22] which may be another mechanism by which CM leads to cognitive impairment. Six months after the episode, impairment was seen in the areas of attention and working memory. Two years after the episode, impairment was seen primarily in the area of attention. Functional neuroimaging studies in children have revealed an overlap in brain processes that are recruited in directed visual attention and in visuospatial working memory. These processes are related to activity in the dorsolateral prefrontal, orbital frontal, and anterior cingulate gyrus areas of the brain.[23] The striking effect of CM in the area of attention, documented at 6-month and 2-year follow-ups, may be attributable to damage to the centrum semiovale. Although detailed imaging studies of CM in children are limited, in 1 pediatric CM case study, a 13-year-old girl had MRI findings consistent with cytotoxic edema of the centrum semiovale.[24] As compared with otherwise healthy children, children with attention-deficit/hyperactivity disorder have elevated N-acetyl-aspartate/creatine ratios in the right prefrontal corticosubcortical region and in the left centrum semiovale on MRI with spectroscopy,[25] suggesting that these areas of the brain may be important in the control of attention. In young children with CM, impairment in attention may therefore be attributable to damage from microvascular sequestration, blood-brain barrier compromise, and immunoreactive processes to the watershed regions that serve the white matter, including the centrum semiovale.[26]

Few clinical or laboratory factors on admission or follow-up were predictive of the risk for long-term cognitive impairment. Hyporeflexia and neurologic sequelae 3 months after discharge both were weakly associated with cognitive impairment at 24 months. The only strong association with cognitive impairment at 24-month follow-up was, not surprising, cognitive impairment at 6-month follow-up. Children who had cognitive deficits 6 months after discharge were more likely to have deficits at 24-month follow-up, but a significant proportion of those with deficits at 24 months (4 of 10) did not have cognitive impairment at the 6-month testing. Thus, in this study, cognitive impairment at 2-year follow-up was not easily predictable by particular clinical or laboratory findings when the child was seen at admission or in follow-up. Given the likely multifactorial nature of the development of long-term cognitive injury in children with CM, it is not surprising that no single clinical or laboratory parameter strongly predicted injury; however, some retrospective studies have

documented an association between specific clinical features (eg, multiple seizures, prolonged coma, depth of coma, hypoglycemia) in CM or malaria with impaired consciousness and subsequent cognitive impairment.[12,27] The larger sample size of these studies may have allowed detection of associations that could not be ascertained in the smaller sample size of this study; however, the retrospective nature of these studies and the significant loss to follow-up of cases in those studies as compared with this study may have also introduced selection bias (eg, children who were more ill during hospitalization may have been more likely to remain in the study area). Larger prospective studies will be required to determine definitively whether specific clinical criteria such as number of seizures or prolonged coma relate to longterm cognitive impairment.

Our study findings confirm those of pioneering retrospective studies of children with antecedent CM or impaired consciousness, which suggested that cognition was impaired in these children long after the CM or impaired consciousness episode (3–9 years later).[4-8,12] These important studies broadened understanding of the potential long-term morbidity of CM; however, although the children with CM were part of a well-studied cohort in several of these studies, control subjects were chosen retrospectively, at the time of cognitive testing (3–9 years after the CM episode). Importantly, assessment of potential confounding factors such as nutrition, home environment, and education level, which can change over time and may be related to long-term cognition, could not be assessed in the studies in the "control" child at the time when the "case" child had CM. In addition, these studies could assess the potential relationship of CM to cognitive deficits 3 to 9 years after the episode but could not track whether these changes were present at earlier periods or changed over time. In this prospective study, assessment of multiple potential confounding factors prospectively allowed for robust estimation of cognitive impairment risk in children with CM, adjusted for these factors. This study also was able to document that the cognitive impairment 6 months after the CM episode is strongly associated with impairment 2 years after the episode (6 [86%] of 7 children with impairment at 6 months had impairment at 2 years), demonstrating that children with CM and early impairment are likely to maintain impairment; however, the study also showed in some children at 2 years cognitive impairment that was not present at 6 months. Thus, children with cognitive impairment 6 months after the CM episode are likely still to have impairment, but it seems that cognitive impairment after CM can also develop later than 6 months after the episode, suggesting that the risk for cognitive impairment increases over time. The primary study limitations are the relatively small sample size and the lack of testing of children who were younger than 5 years. The large CIs for risk estimates of cognitive impairment at both 6 months and 24 months are likely a reflection of the relatively small sample size of this study. Although a larger sample size would have been ideal, the study's excellent follow-up rate (90.1%, excluding children who died during the follow-up period) and the consistent and strong associations of CM with cognitive impairment over time argue in favor of the robustness of study findings, even with a relatively small sample size; however, confirmation of these study findings in larger, preferably multicenter, prospective studies will be important. Future studies should also assess cognition in younger children with CM. Because there is no absolute laboratory or clinical marker for CM, it was impossible to rule out absolutely misdiagnosis; however, our rigorous definition of CM, including the presence of *P falciparum* on blood smear, examination of cerebrospinal fluid to exclude encephalitis or meningitis, assessment of coma by Blantyre or Glasgow coma score, and careful clinical exclusion of other diagnoses, makes it unlikely that CM cases were misdiagnosed. In addition, we documented significantly lower levels of *P falciparum* parasitemia in CC who had asymptomatic parasitemia when compared with children with CM or UM, so the likelihood of incidental parasitemia unrelated to disease is also low. As with all studies of such cohorts, it was impossible to do in-depth testing of cognitive function before the CM episode, because such a study would require cognitive testing of thousands of children, who would then be followed for development of CM; however, very basic screening for developmental delay in the 3 groups showed no

significant difference in the frequency of signs of developmental delay as reported by parents between the groups, and controlling for the reported delay did not alter risk estimates of cognitive impairment. The 3 questions asked were basic and cannot address whether finer level cognition differed among the 3 groups, but we have no a priori reason to suspect that such a difference existed.

CONCLUSIONS

This study provides the first prospective evidence that CM is associated with long-term cognitive deficits. The study findings suggest that CM may be a major cause of cognitive impairment in children in sub-Saharan Africa. Additional work is required to elucidate the mechanisms of central nervous system injury in children with CM as a necessary precursor to development of interventions to prevent long-term cognitive impairment in these children.

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Abbreviations

CM
: cerebral malaria

CC
: community children

UM
: uncomplicated malaria

HOME
: Home Observation for Measurement of the Environment

OR
: odds ratio

CI

confidence interval

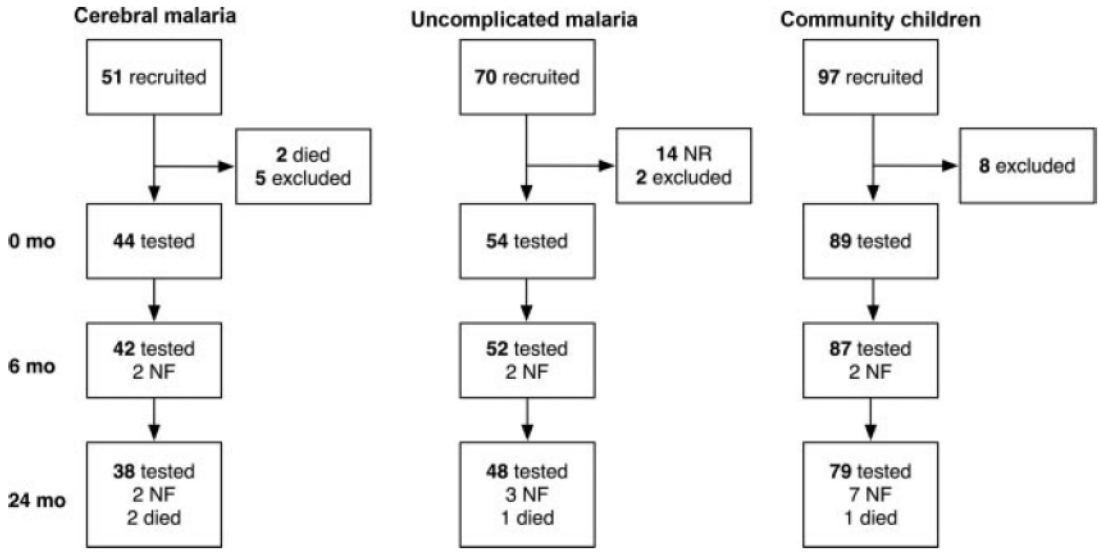

FIGURE 1.

Diagram of number of children tested at enrollment and the 6- and 24-month follow-ups. NR indicates no return (children who had CM and were enrolled at time of episode and did not return for cognitive testing); NF, not found (children who were lost to follow-up).

TABLE 1

Characteristics of the Children With CM or UM and Healthy CC Enrolled at Mulago Hospital, Kampala, Uganda

Characteristic	CM (*n* = 44), Mean (SD)	UM (*n* = 54), Mean (SD)	CC (*n* = 89), Mean (SD)	*P*
Age, y	7.5 (2.1)	8.3 (2.2)	7.9 (2.0)	.17
Height, cm	119.8 (12.5)	125.3 (13.7)	120.8 (12.2)	.07
Weight, kg	22.1 (7.1)	23.4 (6.1)	22.5 (6.2)	.61
Weight for age *z* score	−1.2 (1.6)	−1.2 (1.0)	−1.1 (1.1)	.81
School level	2.6 (2.0)	3.5 (2.3)	3.0 (1.8)	.12
Highest maternal education	6.0 (2.7)	6.1 (2.6)	6.2 (2.2)	.90
Highest paternal education	6.9 (2.5)	7.6 (1.7)	7.1 (2.0)	.33
Socioeconomic status	11.3 (2.8)	12.0 (3.6)	11.0 (2.7)	.23
Home environment score	32.2 (6.3)	33.4 (7.9)	30.7 (7.4)	.11

See text (Clinical and Demographic Characteristics) for scoring of school level, parental education, socioeconomic status, and home environment.

TABLE 2

Frequency of Cognitive Deficits in Children With CM and UM Compared With CC at 24-Month Follow-up

Cognitive Area	CM (*n* = 38), *n* (%)	CC (*n* = 79), *n* (%)	*P*[a]	UM (*n* = 48), *n* (%)	CC (*n* = 79), *n* (%)	*P*[a]
Attention	7 (18.4)	2 (2.5)	.005	0 (0.0)	2 (2.5)	.530
Working memory	3 (7.9)	4 (5.1)	.680	3 (6.3)	4 (5.1)	.999
Tactile learning	3 (7.9)	1 (1.3)	.100	3 (6.3)	1 (1.3)	.150
≥1 Impairment	10 (26.3)	6 (7.6)	.006	6 (12.5)	6 (7.6)	.370

[a] χ^2 test or Fisher's exact test, as appropriate.

TABLE 3

Mean Difference in Cognitive *z* Scores in Children With CM Compared With CC at Enrollment and 6- and 24-Month Follow-ups

Cognitive Area	Enrollment (*n* = 44)		6 mo (*n* = 42)		24 mo (*n* = 38)	
	Mean Difference (95% CI)[a]	*P*[b]	Mean Difference (95% CI)[a]	*P*[b]	Mean Difference (95% CI)[a]	*P*[b]
Attention	−0.57 (−1.07 to −0.07)	.020	−0.38 (−0.82 to 0.06)	.090	−0.71 (−1.10 to −0.32)	<.001
Working memory	−1.15 (−1.61 to −0.69)	<.001	−0.31 (−0.67 to 0.05)	.090	−0.28 (−0.69 to 0.13)	.180
Tactile learning	0.82 (0.28 to 1.36)	.0030	0.23 (−0.17 to 0.64)	.250	0.07 (−0.43 to 0.58)	.780

[a] Adjusted for age, gender, nutrition, home environment score, and child's education levels. Lower scores are worse for attention and working memory; higher scores are worse for tactile learning.

[b] Multiple linear regression analysis.

TABLE 4

Mean Difference in Cognitive *z* Scores in Children With UM Compared With CC at Enrollment and 6- and 24-Month Follow-ups

Cognitive Area	Enrollment (*n* = 54)		6 mo (*n* = 52)		24 mo (*n* = 48)	
	Mean Difference (95% CI)[a]	*P*[b]	Mean Difference (95% CI)[a]	*P*[b]	Mean Difference (95% CI)[a]	*P*[b]
Attention	0.44 (−0.03 to 0.91)	.06	0.28 (−0.13 to 0.71)	.17	−0.03 (−0.40 to 0.34)	.88
Working memory	0.05 (−0.38 to 0.49)	.80	−0.11 (−0.44 to 0.24)	.54	−0.11 (−0.49 to 0.28)	.59
Tactile learning	0.27 (−0.23 to 0.77)	.29	0.22 (−0.15 to 0.61)	.25	0.21 (−0.26 to 0.69)	.38

[a] Adjusted for age, gender, nutrition, home environment score, and child's education levels. Lower scores are worse for attention and working memory; higher scores are worse for tactile learning.

[b] Multiple linear regression analysis.