Long-term Behavioral Problems in Children With Severe Malaria

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abstract

BACKGROUND: Severe malaria in children is associated with long-term neurocognitive impairment, but it is unclear whether it is associated with long-term behavioral problems.

METHODS: Children <5 years old with cerebral malaria (CM) or severe malarial anemia (SMA) treated at Mulago Hospital, Kampala, Uganda were assessed for behavioral outcomes at 0, 6, 12, and 24 months using the Child Behavior Checklist. Sample sizes at 0, 12, and 24 months were 122, 100, and 80 in the CM group, 130, 98, and 81 in the SMA group, and 149, 123, and 90 in healthy community control (CC) children, respectively. Age adjusted z-scores for behavioral outcomes were computed using scores for the CC group. Study groups were compared using regression models adjusted for age, nutritional status, preschool education, and socioeconomic status.

RESULTS: At 12 months, children with SMA had higher z-scores than CC children for internalizing (mean difference, 0.49; SE, 0.14; $P = .001$), externalizing (mean difference, 0.49; SE, 0.15; $P = .001$), and total problems (mean difference, 0.51; SE, 0.15; $P < .001$). Children with CM had higher adjusted z-scores than CC children for externalizing problems (mean difference, 0.39; SE, 0.15; $P = .009$) but not internalizing or total problems. At 24 months, children with CM or SMA both had increased internalizing and externalizing behavioral problems compared with CC children ($P \leq .05$ for all).

CONCLUSIONS: CM and SMA are associated with long-term internalizing and externalizing behavioral problems in children. They may contribute substantially to mental health morbidity in children <5 years old in malaria endemic areas.

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Mr Ssenkusu carried out statistical analyses and interpretation of data, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Hodges conceptualized the initial analysis plan, interpreted the data, and reviewed and revised the manuscript; Drs John and Opoka conceptualized and designed the study, obtained funding, directed the conduct of the study, and reviewed and revised the manuscript; Drs Idro, Shapiro, and Bangirana assisted with the conduct of the study, interpreted the data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Cerebral malaria and severe malarial anemia are associated with long-term neurocognitive impairment in children, but it is unclear if they are associated with long-term behavioral problems.

WHAT THIS STUDY ADDS: This study shows that cerebral malaria and severe malarial anemia are associated with long-term internalizing and externalizing behavioral problems in children.

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In 2015, 88% of the world's malaria cases occurred in Africa. Of the 438 000 estimated malaria deaths, 67% of these were in children under 5 years old.[1] Malaria affects neurocognitive functioning and severe forms of malaria are associated with greater degrees of neurologic and cognitive impairment.[2–5] Cerebral malaria (CM) is the most severe form of malaria, characterized by altered consciousness (Blantyre coma score [BCS] ≤2) and *Plasmodium falciparum* parasitaemia with no other obvious cause of coma.[6–8] Previous studies have documented persistent deficits in attention and working memory in 1 in 4 school-age children 2 years after suffering CM,[9,10] whereas others have documented persistent deficits in speech and language.[2,4,11] However, it is unclear whether behavioral problems are more common in children with CM than in the general population. A recent study by our group showed a greater frequency of mental health disorders and abnormal behavioral scores in children with CM compared with community children,[12] but behavior was assessed with the strengths and difficulties questionnaire,[13] a screening tool that does not provide the in-depth and detailed behavioral assessment provided by the Child Behavior Checklist (CBCL).[14,15] Other studies using the CBCL in Ugandan children showed that behavioral problems were present,[16,17] but did not compare the children to a community control group, whereas a retrospective study in Malawian children using the CBCL showed that behavioral scores did not differ significantly in children with CM compared with control children.[18] Thus, it has been established that behavioral problems are present in children with CM, but it is unclear whether they are more frequent in children with CM than in healthy children in the same community.

Severe malarial anemia (SMA) is another complication of *P falciparum* infection that has been associated with long-term neurocognitive impairment.[19] SMA is far more common than CM, affecting as many as 5 million children every year.[20] However, the long-term effect of SMA on a child's behavior is unknown. A recent study by our group showed similar frequency of mental health disorders between children with SMA and community children.[12] In that study, a behavioral screening tool showed no difference in behavioral disorders in children with CM or SMA as compared with community children, but again, an in-depth assessment of behavior was not performed. To address the gaps in knowledge regarding long-term behavioral outcomes in children with CM or SMA, we conducted a prospective study using a widely used validated behavioral measure, the CBCL, to examine the effect of SMA and CM on behavior among children <5 years old over 24 months.

METHODS

Study Description

This prospective cohort study was performed at Mulago Hospital (Kampala, Uganda) from 2008 to 2014. Children with CM or SMA or community control (CC) children were enrolled if they were between 18 months and 12 years of age. For the current study, we analyzed children between 18 months and 5 years of age, because they were all tested with the preschool CBCL. Children coenrolled in a study of iron treatment in severe malaria[21] were not included in the current study, because iron treatment could affect behavior. CM was defined as: (1) coma (BCS ≤2); (2) *P falciparum* on blood smear; and (3) no other known cause of coma (eg, hypoglycemia-associated coma reversed by glucose infusion, meningitis, or a prolonged postictal state). SMA was defined as the presence of *P falciparum* on blood smears in children with a hemoglobin level ≤5 mg/dL. Hemoglobin was measured by photometry (HemoControl; EKF Diagnostics). The presence of malaria retinopathy was assessed by indirect and direct ophthalmoscopy by trained medical officers at the bedside, using previously established criteria.[22]

CC children were recruited from the nuclear family, neighborhood, or extended family of children with CM or SMA. CC children were chosen to have their age within 1 year of a recently enrolled child with CM or SMA, but were not specifically matched to a child with CM or SMA. Exclusion criteria for all children included: (1) known chronic illness requiring medical care; (2) known developmental delay; (3) previous history of coma, head trauma, or hospitalization for malnutrition or cerebral palsy. Additional exclusion criteria for children with SMA included: (1) impaired consciousness to any degree on physical exam (BCS <5); (2) any other clinical evidence of CNS disease; and (3) repeated seizures before admission. Additional exclusion criteria for CC children included: (1) illness requiring medical care within the previous 4 weeks; and (2) major medical or neurologic abnormalities on screening physical examination.

Children with CM or SMA were managed according to the Ugandan Ministry of Health treatment guidelines current at the time of the study. These included initial intravenous quinine treatment followed by oral quinine for severe malaria while admitted, artemisinin combination therapy for outpatient follow-up therapy, and blood transfusion for all children with SMA.

Written informed consent and assent were obtained from the parents/guardians and children. The Makerere University School of Medicine research and ethics committee and the institutional review boards of Michigan State University and the University of Minnesota approved the study. The Uganda National Council of Science and Technology also reviewed and approved the study.

Behavior Assessment

Children's behavior was assessed at 0 (baseline), 6, 12, and 24 months using the preschool (1.5–5 years) CBCL. Behavioral scores at the 12-month follow-up were chosen preanalysis as the primary study outcome.

The preschool CBCL is a widely used paper-pencil child behavior rating scale that consists of 100 items.[15,23] This checklist is completed by a parent/guardian and the school-age version, with similar items, has shown fair reliability among Ugandan children.[17] It was administered to each child's caregiver (mostly the mothers) at baseline, which was the day of enrolment for the CC children or a week after discharge for children with CM and SMA. Subsequent study visits were done at 6, 12, and 24 months after baseline testing for CC children or after discharge for CM and SMA children. Children were scored on the syndrome scales, which are: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, attention problems, aggressive behavior, and sleep problems. These were summarized into internalizing problems (emotionally reactive, anxious/depressed, somatic complaints, withdrawn), externalizing problems (attention problems, aggressive behavior) and total problems, which included both internalizing and externalizing problems as well as 2 more scales, sleep problems and other problems.[15]

To account for differences in child age and sex, we converted each raw score into a z-score using scores of the CC children. The z-scores were computed as (actual score – mean score for a child's sex and age)/SD, where the mean score for a child's sex and age and SD were computed by fitting a linear mixed effects model to data for all visits for all CC children, and allowing for correlation of visits within a child by including a random effect for the child's intercept. Nutrition (weight-for-age, height-for-age, and weight-for-height) was assessed using the US Centers for Disease Control and Prevention published norms and standardized z-scores.[24] Socioeconomic status was assessed using a checklist of material possessions, housing quality, cooking resources, and water accessibility.[25]

Statistical Methods

Demographic characteristics were compared between groups using the Pearson χ^2 test for categorical measures and one-way analysis of variance for continuous measures. To examine the effect of SMA and CM on child behavior, we compared children surviving SMA and CM to healthy CC children on various behavior summary scores and their subscales. Using z-scores, we first compared children surviving SMA and CM to CC children at the 12-month and 24-month visit by using linear regression models. We then compared the study groups for all 4 time-points simultaneously by testing the group main effect in a mixed linear model allowing correlated errors for children's multiple measurements and repeated interviews for the same caretaker within a child. Correlation of multiple visits within a child was modeled using "xtmixed" in Stata (Stata Corp, College Station, TX). Variation arising from the caretaker interviewed was modeled using a caretaker random effect within child. Because study groups differed in nutrition, preschool education, and socioeconomic status, these characteristics were added to each analysis as adjusters. P values < 0.05 were taken to be significant.

For the SMA and CM groups separately, internalizing, externalizing, and total problems z-scores at 12 months were tested for association with clinical characteristics using the Pearson correlation for continuous measures and 2 sample t tests for binary measures. To account for multiple testing, P values < 0.01 were considered statistically significant. We used Stata, version 12.1 for data analysis.

RESULTS

Demographic Characteristics

We recruited and tested (at baseline) a total of 401 children <5 years of age (130 with SMA, 122 with CM, and 149 CC children). Figure 1 describes the numbers of children who died, were lost to follow-up, or withdrew from the study, and the consequent numbers tested at each time point (baseline, 6, 12, and 24 months). Children with SMA were younger and had lower weight-for-age and height-for-age z-scores than children with CM and CC children. Fewer children with SMA (10%) and CM (15%) had preschool education compared with CC children (32%) (Table 1).

Behavioral Outcomes

We examined behavioral outcomes at 0, 6, 12, and 24 months (Fig 2). On average, children with CM and SMA had higher internalizing, externalizing, and total problem z-scores (an indication of more serious behavioral problems) than CC children. For each behavior z-score, the average score for children with SMA decreased from baseline to 6 months, increased from the 6-month to 12-month follow-up, then decreased markedly at 24 months. Z-scores for children with CM decreased from baseline to 6 months and to 12 months, but increased thereafter at 24 months. The z-scores

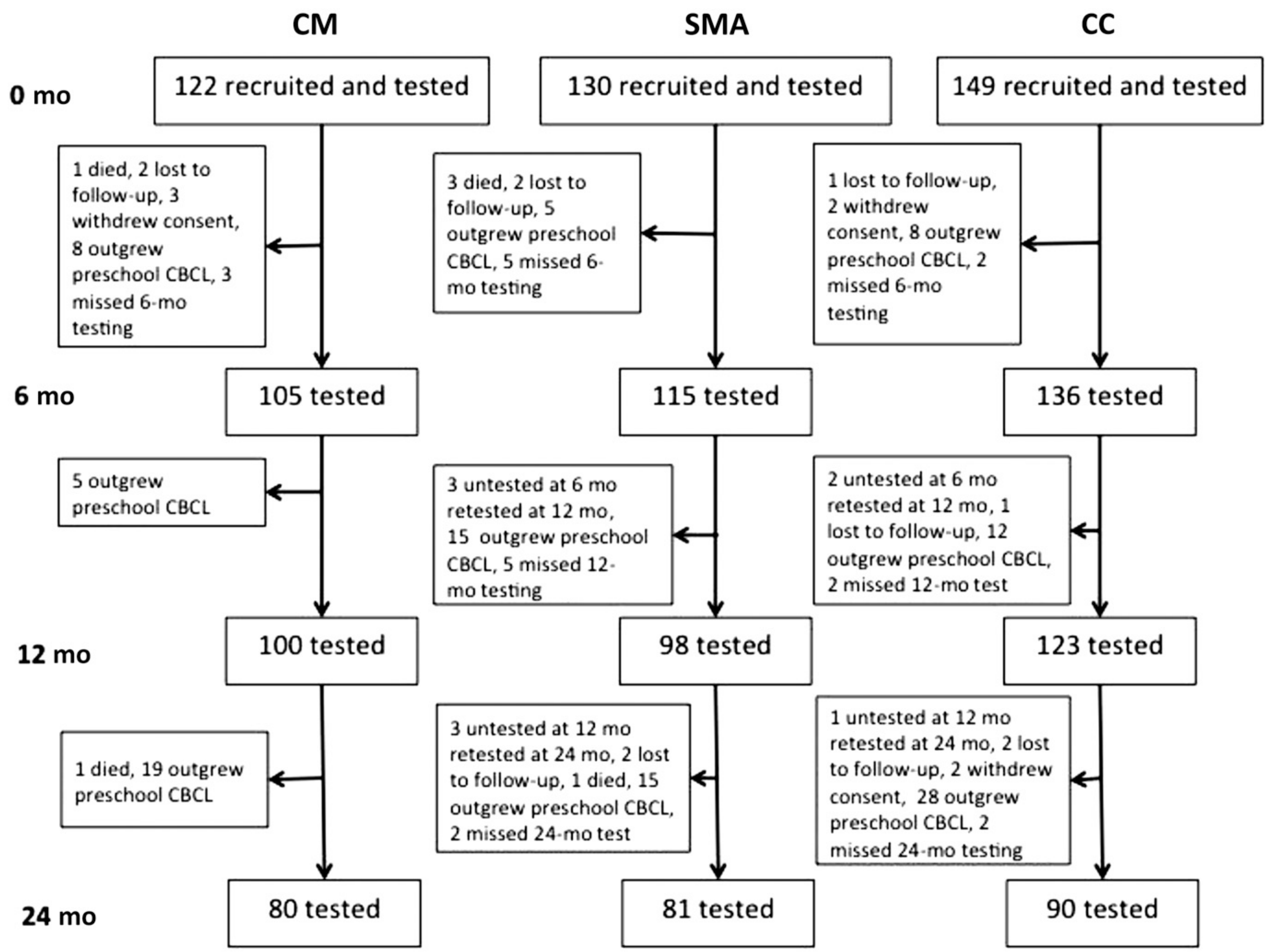

FIGURE 1
Study profile and follow-up testing for the preschool CBCL.

for CC children decreased throughout follow-up.

Children with SMA at 12-months follow-up had significantly higher z-scores than CC children for internalizing (mean difference, 0.49; SE, 0.14; $P = .001$), externalizing (mean difference, 0.49; SE, 0.15; $P = .001$), and total behavioral problems (mean difference, 0.51; SE, 0.15; $P < .001$) after adjusting for nutrition status, preschool education, and socioeconomic status. A similar pattern was present at 24-months follow-up (Table 2). Comparing adjusted scores between children with SMA and CC children using all 4 time points, children with SMA again had higher z-scores for internalizing problems (mean difference, 0.31; SE, 0.09; $P < .001$), externalizing problems (mean difference, 0.29; SE, 0.10; $P = .003$), and total problems (mean difference, 0.34; SE, 0.09; $P < .001$) than CC children.

Children with CM had significantly higher adjusted z-scores than the CC group for externalizing problems (mean difference, 0.39; SE, 0.15; $P = .009$) at the 12-month follow-up visit, and this difference remained significant at the 24-month visit (mean difference, 0.55; SE, 0.17; $P = .001$). At the 24-month follow-up, children with CM also had higher z-scores than the CC group for internalizing problems and total problems, differences not observed at the 12-month follow-up (Table 2). Using all 4 time points, children with CM had higher adjusted z-scores than the CC group for internalizing (mean difference, 0.24; SE, 0.09; $P = .01$), externalizing (mean difference, 0.40; SE, 0.10; $P < .001$) and total problems (mean difference, 0.36; SE, 0.10; $P < .001$). Attrition at 24 months was neither associated with study group ($P = .31$) nor with potential confounders by study group. When considering only children with CM and malaria retinopathy (CM-R), the comparison of children with CM-R to the CC group was quite similar (Supplemental Table 4).

Behavior Subscale Outcomes

We also compared study groups according to syndrome subscales at 12 months and using all 4 time points. Children surviving SMA at 12 months were likely to be more emotionally reactive (mean difference, 0.34; SE, 0.14; $P = .02$), anxious/depressed (mean difference, 0.39; SE, 0.14; $P = .005$), and aggressive (mean difference, 0.50; SE, 0.15; $P = .001$) and to have elevated somatic complaints (mean difference, 0.50; SE, 0.13; $P < .001$) compared with CC children. Children surviving CM at 12 months exhibited elevated aggression (mean difference, 0.43; SE, 0.15; $P = .005$) and somatic complaints (mean difference, 0.45; SE, 0.13; $P = .001$) (Table 3). Using all 4 time points, results were similar to group comparisons at 12 months.

TABLE 1 Demographic Characteristics of Study Children Tested for the Preschool CBCL at 12 Months

Characteristic	CM (*n* = 100)	SMA (*n* = 98)	CC (*n* = 123)	*P*[a]
Age in y, mean (SD)	3.1 (0.8)	2.8 (1.0)	3.3 (0.9)	<.001[b]
Sex, No. female (%)	41 (41)	42 (43)	58 (47)	.63
Weight-for-age z-score, mean (SD)	−1.3 (1.2)	−1.5 (1.6)	−0.9 (1.3)	.002[c]
Height-for-age z-score, mean (SD)	−0.4 (1.3)	−1.1 (1.4)	−1.0 (1.3)	.002[d]
Socioeconomic status score, mean (SD)	8.5 (2.4)	9.5 (3.2)	9.8 (3.2)	.002[e]
Home environment z-score, mean (SD)	0.0 (1.0)	0.0 (0.9)	0.0 (1.0)	.88
Maternal education level, *n* (%)				
Primary 6 or lower	45 (45)	30 (31)	41 (33)	.34
Primary 7	22 (22)	22 (22)	28 (23)	
Secondary or higher	30 (30)	40 (41)	45 (37)	
Not known	3 (3)	6 (6)	9 (7)	
Paternal education level, *n* (%)				
Primary 6 or lower	22 (22)	24 (24)	17 (14)	.21
Primary 7	17 (17)	10 (10)	27 (22)	
Secondary or higher	41 (41)	44 (45)	56 (45)	
Not known	20 (20)	20 (20)	23 (19)	
Child has preschool education, No. (%)	15 (15)	10 (10)	39 (32)	<.001[c]

[a] *P* values are based on one-way analysis of variance for continuous variables and Pearson's χ^2 test for categorical variables. Tukey post-hoc test was used to compare pairs of groups for continuous measures; for child's education, Pearson's χ^2 test was used to compare pairs of groups with a Bonferroni adjustment.
[b] SMA group differs from CC group.
[c] SMA and CM groups differ from CC group.
[d] SMA group differs from CM group and CM differs from CC group.
[e] CM differs from CC group.

Clinical Characteristics

Clinical characteristics assessed as risk factors for adverse behavioral outcomes at 12 months for children with CM or SMA included hypoglycemia (glucose <2.2 mmol/L), use of antimalarial medications before admission, previous seizure or coma history, previous hospitalization, deep respirations, lactic acidosis (lactic acid level ≥5 mmol/L), days of fever, admission temperature, systolic blood pressure, diastolic

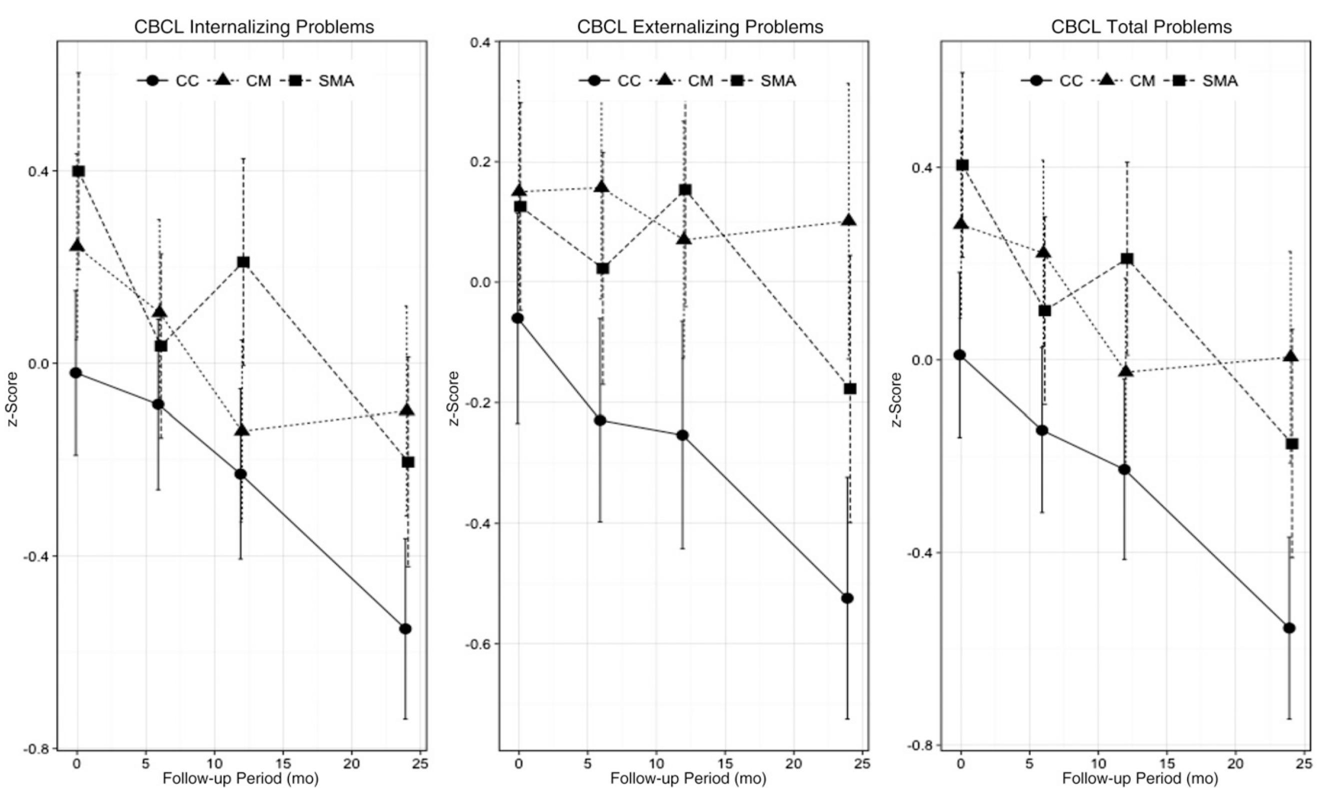

FIGURE 2
Age- and sex-adjusted z-scores in children with CM or SMA and in healthy community control (CC) children <5 years old at 0, 6, 12 and 24 months. Scores are given as unadjusted means with 95% confidence intervals.

TABLE 2 Behavioral Outcome z-Scores in Children With CM or SMA Compared With CC Children at 12 and 24-month Follow-up and Over All Study Visits

CBCL Preschool Scores and Outcomes	CM (n = 100)	SMA (n = 98)	CC (n = 123)	CM − CC		SMA − CC	
				Difference, Mean (SE)	P	Difference, Mean (SE)	P
z-Score at 12 mo, mean (SE)							
Internalizing problems	−0.10 (0.11)	0.23 (0.10)	−0.27 (0.10)	0.16 (0.15)	.27	0.49 (0.14)	.001
Externalizing problems	0.09 (0.11)	0.19 (0.11)	−0.30 (0.10)	0.39 (0.15)	.009	0.49 (0.15)	.001
Total problems	0.01 (0.11)	0.24 (0.11)	−0.27 (0.10)	0.28 (0.15)	.07	0.51 (0.15)	<.001
z-Score at 24 mo, mean (SE)							
Internalizing problems	−0.14 (0.11)	−0.18 (0.11)	−0.49 (0.11)	0.35 (0.16)	.03	0.31 (0.16)	.05
Externalizing problems	0.04 (0.12)	−0.17 (0.12)	−0.51 (0.11)	0.55 (0.17)	.001	0.33 (0.16)	.04
Total problems	−0.05 (0.12)	−0.16 (0.12)	−0.51 (0.11)	0.46 (0.17)	.006	0.35 (0.16)	.04
z-Score for all visits, mean (SE)[a]							
Internalizing problems	0.04 (0.07)	0.12 (0.06)	−0.20 (0.06)	0.24 (0.09)	.010	0.31 (0.09)	<.001
Externalizing problems	0.12 (0.07)	0.01 (0.07)	−0.28 (0.07)	0.40 (0.10)	<.001	0.29 (0.10)	.003
Total problems	0.14 (0.07)	0.12 (0.07)	−0.22 (0.06)	0.36 (0.10)	<.001	0.34 (0.09)	<.001

Mean z-score differences at 12 and 24 months for CM minus CC and SMA minus CC were adjusted for nutrition status (weight-for-age and height-for-age), preschool education, and socioeconomic status; mean z-score differences using all visits for CM minus CC and SMA minus CC were adjusted for time, nutrition status, preschool education, and socioeconomic status. Age- and sex-adjusted CBCL z-scores were computed using CC children as the reference population.

[a] Mixed linear model estimates of mean z-scores at enrollment and at the 6-, 12-, and 24-month visits. Some children had different caretakers at different visits; a random effect for caretaker allowed scores within a child from the same caretaker to be more highly correlated than scores from different caretakers.

TABLE 3 Behavioral Outcome Subscale z-Scores in Children With CM or SMA Compared With CC Children at 12-Month Follow-up and Over All Study Visits

CBCL Preschool Scores and Outcomes	CM (n = 100)	SMA (n = 98)	CC (n = 123)	CM − CC		SMA − CC	
				Difference, Mean (SE)	P	Difference, Mean (SE)	P
z-Score at 12 mo, mean (SE)							
Internalizing problems							
Emotionally reactive	−0.15 (0.11)	0.21 (0.10)	−0.13 (0.10)	−0.02 (0.15)	.90	0.34 (0.14)	.02
Anxious/depressed	−0.21 (0.10)	0.13 (0.10)	−0.26 (0.09)	0.05 (0.14)	.71	0.39 (0.14)	.005
Somatic complaints	0.12 (0.09)	0.17 (0.09)	−0.33 (0.09)	0.45 (0.13)	.001	0.50 (0.13)	<.001
Withdrawn	0.00 (0.12)	0.17 (0.12)	−0.07 (0.11)	0.07 (0.16)	.67	0.24 (0.16)	.14
Externalizing problems							
Attention problems	−0.08 (0.09)	0.06 (0.09)	−0.17 (0.08)	0.09 (0.13)	.50	0.23 (0.13)	.08
Aggressive behavior	0.13 (0.11)	0.20 (0.11)	−0.30 (0.10)	0.43 (0.15)	.005	0.50 (0.15)	.001
z-Score for all visits, mean (SE)[a]							
Internalizing problems							
Emotionally reactive	0.01 (0.07)	0.12 (0.06)	−0.12 (0.06)	0.13 (0.09)	.16	0.24 (0.09)	.005
Anxious/depressed	−0.05 (0.06)	0.04 (0.06)	−0.19 (0.06)	0.13 (0.09)	.12	0.23 (0.08)	.006
Somatic complaints	0.09 (0.06)	0.07 (0.06)	−0.21 (0.06)	0.30 (0.09)	.001	0.28 (0.08)	.001
Withdrawn	0.09 (0.07)	0.11 (0.07)	−0.07 (0.06)	0.16 (0.10)	.09	0.18 (0.09)	.05
Externalizing problems							
Attention problems	−0.08 (0.06)	−0.06 (0.05)	−0.20 (0.05)	0.12 (0.08)	.13	0.14 (0.07)	.05
Aggressive behavior	0.17 (0.08)	0.04 (0.07)	−0.26 (0.07)	0.43 (0.10)	<.001	0.29 (0.10)	.002

Mean z-score differences at 12 months for CM minus CC and SMA minus CC were adjusted for nutrition status (weight-for-age and height-for-age), preschool education, and socioeconomic status; mean z-score differences using all visits for CM minus CC and SMA minus CC were adjusted for time, nutrition status, preschool education, and socioeconomic status. Age- and sex-adjusted CBCL subscale z-scores were computed using CC children as the reference population.

[a] Mixed linear model estimates of mean z-scores at enrollment and at 6-, 12-, and 24-month visits. Some children had different caretakers at different visits; a random effect for caretaker allowed scores within a child from the same caretaker to be more highly correlated than scores from different caretakers.

blood pressure, pulse on admission, hemoglobin level at admission, white blood cell count, and platelet count. Additional factors assessed for children with CM included abnormal posturing, presence and number of seizures before admission, BCS score, presence and number of seizures after admission, and coma duration. For both children with CM or SMA, no clinical characteristics were associated with behavioral outcomes (using $P < .01$ as the threshold for significance to account for the multiple predictors being assessed) (Supplemental Tables 5 and 6).

DISCUSSION

The current study provides the most rigorous evidence to date that CM is associated with long-term behavior problems and documents the novel finding that SMA is also associated with long-term behavior problems, a finding of particular public health importance because SMA is estimated to affect as many as 5 million African children annually.[20]

Children with SMA had no clinically apparent neurologic involvement yet had persistent behavioral problems at 12 and 24 months after the SMA episode. Both externalizing and internalizing behavior scores were higher, indicating more problematic behavior, in children with SMA than in CC children. It is unclear why children with SMA develop behavioral problems. No specific clinical risk factors were identified in the current study. One possibility is that the association between SMA and behavioral problems reflects the effects of iron deficiency, which is common in children with severe malaria.[26,27] A study that investigated the effect of iron deficiency in infancy on executive function and recognition at 19 years found that participants with chronic, severe iron deficiency performed poorly on executive functions, including inhibitory control, set shifting, and planning.[28] Iron-deficient infants have been characterized as maintaining a closer contact with their mothers, being less attentive and less playful, and showing less pleasure and delight,[29,30] all of which are symptoms of internalizing problems. Lozoff et al[31] showed that iron deficient children in infancy were more likely to have internalizing and externalizing problems in their early adolescence than children who were free of iron deficiency during infancy. Children with SMA in the current study showed similar behavioral problems, with increased (worse) scores for emotional reactivity, anxiety/depression, aggression, and somatic complaints, all behaviors consistent with iron deficiency. We did not assess iron deficiency in the current study, but are conducting ongoing studies to determine the relationship between iron deficiency and behavior in children with SMA. Acute or chronic cerebral hypoperfusion or ischemia may accompany anemia,[32] although there is limited data outside of sickle cell disease and stroke to support this association. If anemia leads to cerebral ischemia, it could also lead to behavioral problems,[33] although the mechanisms of occurrence still require investigation.

The presence and severity of behavioral problems among children with CM has been assessed in past studies, but with conflicting or incomplete results. Previous studies by our group have documented behavioral problems in children with CM, but did not assess whether they were more frequent or of greater severity than in healthy children in the same community.[16,17,34] One prospective study of Ugandan children with malaria with neurologic involvement (including 9 children with CM) did show increased internalizing problem scores in these children compared with community controls,[35] but a larger retrospective study of Malawian children with CM showed no difference in behavior scores between children with CM and community controls.[18] The Malawi study included only children with CM-R, whereas the current study included all children with CM, but it is unlikely that retinopathy is the explanation for the differences in study findings, because behavior differences were still seen in the current study when analysis was restricted to CM-R children. The current study, a prospective assessment of behavioral outcomes over multiple time points, provides the strongest evidence to date that behavioral problems are greater in children with CM than in healthy children in the same community, and that the behavioral problems persist over time.

Behavioral problems in CM and SMA groups could also be a consequence of admission for life-threatening illnesses involving invasive procedures. Two systematic reviews of psychological outcomes after admission in a pediatric ICU found that behavior problems are common, including posttraumatic stress disorder and depression.[36,37] The child’s age, length of hospital stay, parents' distress, delusional memories, premorbid psychopathology, and number of invasive procedures were associated with psychological outcomes.[36,37] Although we did not find demographic or clinical predictors of behavioral outcomes in the current study, it is possible that the intensive care and invasive procedures experienced by the children played a role in their subsequent development of behavioral problems.

Child education and nutritional status as well as fewer nutritional resources in a child’s home environment have also been associated with lower cognitive ability.[5,25,38] In this study, after adjusting for preschool education, nutrition status, and socioeconomic status, children with SMA and CM still showed a higher degree of behavioral problems than the CC children. These behavioral problems are therefore more likely a result of the malaria and not these socioeconomic variables.

A limitation of our study is that parents/caretakers were not blinded to the group the child belonged to and may have overreported symptoms, especially for children who had experienced SMA or CM. We did not assess study participants for iron deficiency, which is associated with behavioral problems in children, so we cannot fully explain the observed greater degree of behavioral problems after SMA. Study children did not have their behavior rated before their illness, making it impossible to know their previous premorbid functioning. However, we did compare their behavior to control children, who were recruited from their household or neighborhood and served as a proxy for premorbid functioning.

In conclusion, both SMA and CM are associated with long-term internalizing and externalizing behavior problems. Future studies should investigate the factors that may lead to behavior problems in these children, including iron deficiency. Although interventions to prevent behavioral problems in children with CM or SMA are being assessed, psychosocial interventions aimed at reducing distress in caregivers of admitted children could potentially enhance long-term behavioral outcomes in children who have previously suffered CM or SMA.[39] Interventions to prevent, ameliorate, or treat behavioral problems in children with severe malaria have the potential for a major public health impact in sub-Saharan Africa.

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ABBREVIATIONS

BCS: Blantyre coma score
CBCL: child behavior checklist
CC: community control
CM: cerebral malaria
CM-R: CM and malaria retinopathy
SMA: severe malarial anemia

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