RESEARCH ARTICLE

Admission Clinical and EEG Features Associated With Mortality and Long-term Neurologic and Cognitive Outcomes in Pediatric Cerebral Malaria

Daniel J. Clark, MD, PhD, Caitlin Bond, MPH, Alexander Andrews, MD, Daniel J. Muller, MPhil, Angela Sarkisian, BS, Robert O. Opoka, MMED, PhD, Richard Idro, MBChB, MMED, PhD, Paul Bangirana, PhD, Andy Witten, MD, Nicholas J. Sausen, MD, Gretchen L. Birbeck, MD, MPH, DTMH, Chandy C. John, MD, MS,* and Douglas G. Postels, MD, MS*

Correspondence
Dr. Clark
daniel.clark@cchmc.org

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Abstract

Background and Objectives

For children with cerebral malaria, mortality is high, and in survivors, long-term neurologic and cognitive dysfunctions are common. While specific clinical factors are associated with death or long-term neurocognitive morbidity in cerebral malaria, the association of EEG features with these outcomes, particularly neurocognitive outcomes, is less well characterized.

Methods

In this prospective cohort study of 149 children age 6 months to 12 years who survived cerebral malaria in Kampala, Uganda, we evaluated whether depth of coma, number of clinical seizures, or EEG features during hospitalization were associated with mortality during hospitalization, short-term and long-term neurologic deficits, or long-term cognitive outcomes (overall cognition, attention, memory) over the 2-year follow-up.

Results

Higher Blantyre or Glasgow Coma Scores (BCS and GCS, respectively), higher background voltage, and presence of normal reactivity on EEG were each associated with lower mortality. Among clinical and EEG features, the presence of >4 seizures on admission had the best combination of negative and positive predictive values for neurologic deficits in follow-up. In multivariable modeling of cognitive outcomes, the number of seizures and specific EEG features showed independent association with better outcomes. In children younger than 5 years throughout the study, seizure number and presence of vertex sharp waves were independently associated with better posthospitalization cognitive performance, faster dominant frequency with better attention, and higher average background voltage and faster dominant background frequency with better associative memory. In children younger than 5 years at CM episode but 5 years or older at cognitive testing, seizure number, background dominant frequency, and the presence of vertex sharp waves were each associated with changes in cognition, seizure number and variability with attention, and seizure number with working memory.

Discussion

In children with cerebral malaria, seizure number is strongly associated with the risk of long-term neurologic deficits, while seizure number and specific EEG features (average background voltage, dominant rhythm frequency, presence of vertex sharp waves, presence of variability) are independently associated with cognitive outcomes. Future studies should evaluate the predictive value of these findings.

*These authors contributed equally to this work as co-senior authors.

From the Division of Neurology (D.J.C.), Nationwide Children's Hospital, Columbus, OH; Ryan White Center for Pediatric Infectious Diseases & Global Health (C.B., C.C.J.), Indiana University School of Medicine, Indianapolis; Department of Pediatrics (A.A.), MedStar Georgetown University Hospital; The George Washington University School of Medicine and Health Sciences (D.J.M., A.S., D.G.P.), Washington, DC; Department of Paediatrics and Child Health (R.O.O., R.I.), Makerere University College of Health Sciences; Department of Psychiatry (P.B.), Makerere University College of Health Sciences, Kampala, Uganda; Department of Neurosurgery (A.W.), Indiana University School of Medicine, Indianapolis; Department of Pediatrics (N.J.S.), Division of Emergency Medicine, University of Minnesota, Minneapolis; Department of Neurology (G.L.B.), University of Rochester, NY; University of Zambia (G.L.B.), School of Medicine, Lusaka; University Teaching Hospitals Children's Hospital (G.L.B.), Lusaka, Zambia; Children's National Medical Center (D.G.P.), Washington, DC; and Blantyre Malaria Project (D.G.P.), Kamuzu University of Health Sciences, Blantyre, Malawi.

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Glossary

BCS = Blantyre Coma Score; **CM** = cerebral malaria; **GCS** = Glasgow Coma Score; **KABC** = Kaufman Assessment Battery for Children; **LME** = linear mixed-effects.

Introduction

Malaria kills more than 600,000 people annually, most of them were younger than 5 years.[1] Infection may result in clinical syndromes ranging from asymptomatic parasitemia, uncomplicated malaria (a flu-like illness), to severe malaria with end-organ dysfunction. The most lethal form of severe disease is cerebral malaria (CM), defined as an otherwise unexplained coma in someone with asexual forms of *Plasmodium* parasitemia. Untreated, CM is universally fatal.[2] With prompt and optimal treatment, mortality rates vary from 15% to 25%.[3-5] Clinical seizures are very common both before and during hospitalization.

Multiple studies have established associations between biomarkers or clinical factors and mortality in pediatric CM. Clinical risk factors for death include deeper coma (Blantyre Coma Score [BCS, a measure of coma depth used in young children across Africa] ≤ 1), leukocytosis, hypoglycemia, hyperlactatemia, and papilledema.[4-9] Diffuse brain swelling on brain MRI,[5] low flow on transcranial Doppler ultrasound,[10] and certain features on admission EEG[5,11]—focal or background slowing, low amplitudes, lack of reactivity, and absence of normal sleep architecture—are associated with death in children with CM.

In CM survivors, neurologic and cognitive deficits are common. At hospital discharge, 10%–30% of survivors have gross neurologic abnormalities.[12] Deficits may resolve or appear after hospitalization. Long-term, 25%–50% have neurodevelopmental impairments[13,14] and 9%–17% have epilepsy.[15-17] Previously described neurodevelopmental sequelae include visual impairment, motor abnormalities, ataxia, language regression, cognitive impairment, and behavioral problems.[11-29] Lower average voltage and lower variability of fast frequencies on admission EEG are associated with neurologic deficits at the time of discharge.[11,30,31] In brain MRI acquired at 1 month postdischarge, atrophy and multifocal signal abnormalities are seen in children who had deficits at discharge.[14,26]

Although various clinical factors are associated long-term adverse outcomes in CM survivors—repeated seizures prior to or during hospitalization, admission depth of coma, higher maximum temperature, male sex, and the presence of focal neurologic deficits at hospital discharge[13,14,17,26]—comparatively few biomarkers have been investigated to this end. The association of EEG features with long-term cognitive outcomes has not been characterized to date. Knowledge of EEG features associated with adverse long-term cognitive outcomes may aid in identifying high-risk children most in need of cognitive training and rehabilitation. To evaluate whether admission EEG features are associated with mortality or adverse long-term neurologic or cognitive outcomes in children with CM, we compared clinical findings and EEG features on admission in a cohort of Ugandan children with CM to in-hospital mortality, short-term and long-term neurologic deficits, and long-term cognitive outcomes over a 2-year follow-up period.

Methods

Study Enrollment, Clinical Care, and Evaluation

Children age 6 months to 12 years with a diagnosis of CM (defined as coma with BCS ≤2 or Glasgow Coma Score [GCS] ≤8, blood smear positive for *Plasmodium falciparum*, and lack of alternative etiology for coma) admitted to Mulago Hospital (Kampala, Uganda) between 2008 and 2013 were eligible for inclusion in this prospective cohort study. Children were excluded if they had a history of developmental delay, cerebral palsy, head trauma, coma, malnutrition requiring hospitalization, or other chronic illness requiring persistent medical care. The history of seizures was not an exclusion criterion. Participants received specific and supportive care according to standard guidelines for severe malaria in Uganda at that time. Intravenous quinine (20 mg/kg loading dose followed by 10 mg/kg every 8 hours for a minimum 3 doses or until the child was able to take orally) was immediately administered on CM diagnosis. The BCS for children younger than 5 years[4] or GCS for children older than 5 years was assessed by a clinician. Parents, caregivers, or nurses notified the study medical officers about clinical seizures after admission, and the number of these seizures was recorded. We defined a seizure as nonsuppressible, repeated tonic-clonic movements. Clinical seizures were treated with a maximum of 2 doses intravenous diazepam, followed by a loading dose of intravenous phenobarbital 15 mg/kg plus additional escalation if needed. Some children received antiseizure medication before EEG performance.

EEG Acquisition and Interpretation

A 30-minute EEG, performed using the standard 10–20 system, was acquired after initial clinical stabilization, generally within 4 hours of hospital admission. Recordings were obtained on an XLTEC 32 channel machine (Natus Medical Corporation, Pleasanton, CA) with a sampling rate of 200 Hz. EEG tracings were interpreted in real time to identify electrographic seizures or nonconvulsive status epilepticus. After hospital discharge, research interpretations by visual inspection (used in this study) were performed by a board-certified pediatric neurologist, blinded to patient outcome, using Persyst software (Persyst Corporation, Prescott, AZ).

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Neurologic and Cognitive Assessments

In survivors, physical and neurologic examinations, and/or neurocognitive testing, were performed at hospital discharge (neurologic examination), 1 week after discharge (neurocognitive testing only), and 6, 12, and 24 months later (all evaluations) (eFigure 1, links.lww.com/WNL/D28). We defined a neurologic deficit as the presence of a motor or cranial nerve abnormality, ataxia, movement, speech, or visual problems. Cognitive outcomes were assessed using standardized testing tools previously validated for evaluation in Ugandan children. In children younger than 5 years, we measured overall cognition as a composite score of the fine motor, visual reception, and receptive and expressive language scales on the Mullen Scales of Early Learning.[e1] We assessed attention using the Early Childhood Vigilance Test.[e2] Associative memory was assessed using the Color Object Association Test.[e3]

In children 5 years and older, we measured overall cognition using the Kaufman Assessment Battery for Children (KABC),[e4] with a summary mental processing index as the primary outcome. Attention was assessed using the Test of Variables of Attention,[e5] with D prime measure as the primary outcome. We used the KABC-2 subtest for sequential processing to assess working memory. Emotional stimulation in the home was measured by age-appropriate versions of the Home Observation for the Measurement of the Environment.[e6]

We calculated age-adjusted z-scores for neuropsychological testing outcomes using aged-matched community controls.[32] Z-scores were calculated using the patient's score minus the mean community control score for a child's age. We computed standard deviations by fitting a quadratic mixed-effects model, including a random intercept for the child. Owing to repeated testing, correlations within an individual were based on time between visits, considering all visits for community control children.

Statistical Analysis

Descriptive statistics are presented as median values with interquartile range for continuous measures and proportions for categorical measures. We assessed the association of baseline demographic, clinical, or EEG features with in-hospital mortality by logistic regression. We assessed the association of seizure number, BCS/GCS, and EEG features with neurologic deficits over a 24-month follow-up period using logistic regression with Firth penalized likelihood procedure[e7] because of a low number of neurologic deficits during follow-up. We assessed the association of EEG features with longitudinal changes in cognitive z-scores over time using a linear mixed-effects (LME) model adjusted for age, socioeconomic status, home environment z-score, and antiseizure medication administration before EEG, where observations within subject were correlated using a subject-specific intercept, and time points were treated as categorical variables.[33] The LME models used a banded diagonal covariance matrix to model within-subject variance-covariance errors. We fitted the mixed model by restricted maximum likelihood and used Kenward-Roger approximations to estimate the denominator degrees of freedom.

To further characterize how coma score, seizure number, and EEG features related to neurologic deficit at testing time points, we evaluated negative and positive predictive values for each factor and area under the curve for nonparametric receiver operating characteristic curves. To determine whether EEG features and seizure number were independently associated with long-term cognitive outcomes, we constructed multivariable regression models that included the number of clinical seizures and EEG features associated with cognitive outcomes in univariable analysis, choosing p value of ≤0.05 as significant. To correct for multiplicity, the Benjamini-Hochberg false discovery rate procedure[e8] was used. Analyses were performed using Stata version 16.1 (StataCorp, College Station, TX). Please see supplementary material for references to testing instruments and statistical tools.

Standard Protocol Approvals, Registrations, and Patient Consents

Parents or guardians of study participants gave written informed consent. Institutional Review Boards at Michigan State University, University of Minnesota, and Makerere University School of Medicine granted ethical approval.

Data Availability

Anonymized data not published within this article will be made available by request from a qualified investigator.

Results

Study Participant Enrollment, Follow-up, and Neurologic Deficits

Of the 269 children admitted with CM, 176 had EEGs (eFigure 1, links.lww.com/WNL/D28). Ninety-three children with CM did not have EEG analysis performed because they awakened before EEG performance or an EEG technician was not available, so an EEG was not performed, or because their level of consciousness during the EEG was not noted. Of the 176 children who had an EEG on admission, 27 died. All 149 survivors returned for 1-week postdischarge follow-up. At the time of hospital discharge, the median age of survivors was 3.5 years, 64% were male, and 41% (61/148) had abnormal neurologic examinations. The rate of abnormal neurologic examinations decreased to 7.5% (11/146), 4.8% (7/145), and 4.2% (6/142) at the 6-, 12-, and 24-month follow-up time points, respectively. Follow-up was outstanding, with 142 of the 149 survivors of CM (95.3%) followed all the way through 2-year follow-up. All children with neurologic deficits at later time points had deficits at prior time points.

Association of Coma Score, Clinical Seizures, and EEG Features With Mortality

A higher BCS or GCS was associated with lower mortality (BCS, OR, 0.45, 95% CI 0.23, 0.88, $p = 0.02$; GCS, OR 0.35, 95% CI 0.13, 0.95, $p = 0.04$) (Figure 1). Among EEG features,

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higher average voltage (log_{10}-transformed) (OR 0.05; 95% CI 0.01, 0.36; $p = 0.003$) and the presence of reactivity (OR 0.26, 95% CI 0.08, 0.81; $p = 0.02$) were associated with lower mortality.

Associations of Clinical Seizures, Coma Score, and EEG Features With Neurologic Deficits Over Time

The number of seizures during admission was associated with neurologic deficits at 6, 12, and 24 months, with stronger associations over time (Figure 2). Having 4 or more seizures vs < 4 seizures was more strongly associated with neurologic deficits than a lower seizure number, whereas having 5 or more seizures did not discriminate better than have 4 or more seizures (eTable 1, links.lww.com/WNL/D28). A higher BCS was associated with a lower risk of neurologic deficits at the 6-, 12-, and 24-month time points (Figure 2). Too few older children (in whom GCS was used) had long-term neurologic deficits to allow evaluation of the association of GCS with neurologic deficits.

Among EEG features, lower average voltage, slower dominant frequency, and the presence of asymmetry, epileptiform discharges, or electrographic seizures were all associated with neurologic deficits at the 6-, 12-, and 24-month follow-up (Figure 3). Because clinical evaluations would rely on negative and positive predictive value of specific factors, we evaluated dichotomized values for BCS (<2 vs 2), seizure number (>4 vs ≤4), average background voltage (<50 vs ≥50 microvolt), dominant frequency (<2.5 vs ≥2.5 Hz), and asymmetry (yes vs no). Seizure number had the best positive predictive values for neurologic deficits in follow-up among all clinical or EEG features and had high negative predictive values like those of BCS or EEG features (Table 1).

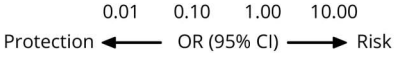
Association of the Number of Clinical Seizures and Coma Score With Cognitive Outcomes

We evaluated whether clinical features (e.g., number of seizures, coma score) were associated with cognitive outcomes. Higher seizure number was associated with worse cognition and attention in children younger than 5 years at CM episode and worse cognition, attention, and associative memory in children younger than 5 years at CM episode but 5 years or older at testing time. Higher seizure number was not associated with any cognitive outcome in children 5 years or older at CM episode (Table 2). Cutoffs of 4+ or 5+ seizures (compared with <4 or <5 seizures, respectively) had similarly strong associations with cognitive outcomes in children younger than 5 years, and the associations with these cutoffs were stronger than with lower numbers of seizures (eTable 2, links.lww.com/WNL/D28).

Higher admission BCS was associated with better overall cognitive ability in children younger than 5 years at CM episode, and better attention and memory in children younger than 5 years at CM episode but 5 years or older at testing time. Higher GCS was not associated with improved cognitive outcomes in any domain in children 5 years or older at CM episode (Table 2). In cognitive outcome evaluation, BCS and number of seizures were collinear, so an analysis of whether

Figure 1 Associations Between Demographic, Clinical, and EEG Characteristics and Mortality

	CM deceased (n = 27)		CM survived (n = 149)		Odds ratio (95% CI)	*p* value[b]
	N	Median (IQR)[a]	N	Median (IQR)[a]		
Demographic characteristics						
Age (years)	27	2.5 (2.1, 4.5)	149	3.5 (2.6, 4.4)	0.87 (0.69, 1.11)	0.28
Sex, male, n (%)	27	13 (48.2)	149	96 (64.4)	0.51 (0.22, 1.18)	0.11
Clinical characteristics						
Blantyre coma score (<5 years)	22	1 (1, 2)	116	2 (1, 2)	0.45 (0.23, 0.88)	0.02
Glasgow coma score (≥5 years)	5	6 (5, 7)	34	7 (7, 8)	0.35 (0.13, 0.95)	0.04
Seizures prior to admission	27	3 (2, 6)	148	4 (2, 6)	0.99 (0.90, 1.10)	0.92
Seizures after admission	27	1 (0, 2)	149	1 (0, 2)	1.06 (0.92, 1.22)	0.42
Electroencephalogram characteristics						
Average background voltage, V[e]	23	50 (40, 80)	145	70 (50, 90)	0.09 (0.01, 0.61)	0.01
Dominant frequency, Hz	23	1.5 (1.0, 2.5)	143	2.0 (1.5, 2.5)	0.60 (0.34, 1.07)	0.09
Vertex sharp waves, n (%)	27	8 (29.6)	145	57 (39.3)	0.65 (0.27, 1.58)	0.34
Sleep spindles, n (%)	27	12 (44.4)	145	88 (60.7)	0.52 (0.23, 1.19)	0.12
Normal reactivity, n (%)	25	4 (16.0)	132	55 (41.7)	0.27 (0.09, 0.82)	0.02
Paradoxical reactivity, n (%)	4	3 (75.0)	55	51 (92.7)	0.24 (0.02, 2.81)	0.25
Asymmetry, n (%)	27	2 (7.4)	145	20 (13.8)	0.50 (0.11, 2.28)	0.37
Variability, n (%)	27	14 (51, 9)	146	97 (66.4)	0.54 (0.24, 1.25)	0.15
Epileptiform discharges, n (%)	27	2 (7.4)	149	20 (13.4)	0.52 (0.11, 2.35)	0.39
Electrographic seizures, n (%)	27	1 (3.7)	149	11 (7.4)	0.48 (0.06, 3.90)	0.49



[a]Except where noted, [b]Logistic regression model, [c]Adjusted for whether child was on antiseizure medication before EEG, [d]Log(base 10)-transformed for regression. Forest plot shows odds ratios and 95% CI of those who died vs survived, where red indicates a significant association between characteristic and protection of in-hospital mortality.

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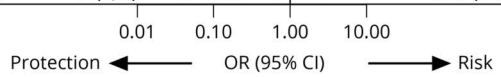
Figure 2 Association of Number of Seizures Before or During Admission or Blantyre Coma Score and Neurologic Deficits Over Time

Clinical characteristics		With neurologic deficit N	With neurologic deficit Median (IQR)	Without neurologic deficit N	Without neurologic deficit Median (IQR)	Odds ratio (95% CI)	*p* value[a]
Number of seizures before admission	Discharge	61	4 (2, 6)	86	4 (2, 6)	1.04 (0.96, 1.13)	0.34
	6 months	11	4 (2, 5)	134	4 (2, 6)	1.00 (0.85, 1.16)	0.96
	12 months	7	3 (1, 4)	137	4 (2, 6)	0.86 (0.64, 1.15)	0.31
	24 months	6	3 (1, 4)	136	4 (2, 6)	0.86 (0.63, 1.18)	0.36
Number of seizures after admission/during hospitalization	Discharge	61	0 (0, 2)	87	1 (0, 2)	1.06 (0.93, 1.21)	0.39
	6 months	11	1 (0, 8)	135	1 (0, 2)	1.43 (1.10, 1.86)	**0.01***
	12 months	7	5 (0, 9)	138	1 (0, 2)	1.53 (1.15, 2.03)	**0.003***
	24 months	6	7 (0, 9)	136	1 (0, 2)	1.63 (1.21, 2.19)	**0.001***
Blantyre coma score (<5 years)	Discharge	47	2 (1, 2)	68	2 (1, 2)	0.66 (0.35, 1.24)	0.20
	6 months	10	1 (1, 1)	104	2 (1, 2)	0.21 (0.08, 0.59)	**0.003***
	12 months	6	1 (1, 1)	107	2 (1, 2)	0.24 (0.07, 0.79)	**0.02***
	24 months	5	1 (1, 1)	105	2 (1, 2)	0.16 (0.04, 0.62)	**0.01***



[a]Binary logistic regression using Firth penalized likelihood procedure. Red indicates significant association between clinical characteristic and protection or risk of neurologic deficit at each time point before correction for multiplicity. *Significant *p* value after correction for multiple comparisons using Benjamini-Hochberg false discovery rate approach.

BCS and number of seizures were independently associated with cognitive outcomes was not possible.

Association of EEG Features With Cognitive Outcomes

Finally, we evaluated associations of EEG features with cognitive outcomes. Among continuous EEG features, higher average background voltage and faster dominant frequency were associated with better cognitive outcomes in one or more domains in children younger than 5 years at the time of CM episode, whether tested at younger than 5 or 5 years or older at the time of follow-up testing. Neither amplitude nor frequency was associated with cognitive outcomes in children younger than 5 years at the time of CM episode (Table 3). Among categorical EEG variables, the presence of variability was associated with significantly higher attention scores, and asymmetry with significantly lower scores, in children younger than 5 years at CM episode but 5 years or older at the follow-up testing (Table 3).

Multivariable Model of Association of Clinical and EEG Features With Cognitive Outcomes

To determine whether clinical variables (seizure number) and EEG features were independently associated with cognitive outcomes, we conducted multivariable analysis, including all features associated in univariable analysis in the multivariable model (BCS was again not included because of collinearity with seizure number, and electrographic seizures and epileptiform discharges were not included because they were strongly associated with asymmetry). Among children younger than 5 years on admission and in follow-up, fewer clinical seizures and the presence of vertex sharp waves were independently associated with higher overall cognition scores, higher dominant frequency with better attention scores, higher average background voltage, and higher dominant frequency with better associative memory scores (Table 4).

Among children younger than 5 years on admission but 5 years or older in follow-up, fewer clinical seizures, faster dominant frequency, and the presence of vertex sharp waves were each independently associated with higher cognition scores. Fewer clinical seizures and the presence of variability were associated with higher scores on measures of attention. An increased number of seizures were associated with lower associative memory test scores (Table 4).

Multivariable models were not constructed for cognitive outcomes in children 5 years or older because the number of clinical seizures was not associated with any cognitive outcomes in this age group.

A schematic of clinical and EEG features that were associated with mortality, neurologic deficits over follow-up, or long-term cognition scores is presented in eFigure 2, links.lww.com/WNL/D28.

Discussion

In this study, we show for the first time that in children with CM, the clinical finding of the number of postadmission seizures and specific EEG features on admission are each independently associated with long-term cognitive outcomes, while seizure number alone, an easily assessable clinical parameter, is strongly

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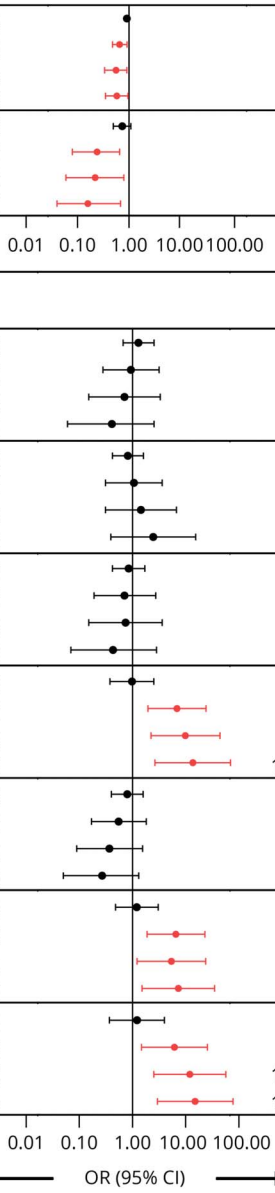
Figure 3 Association Between EEG Features and Neurologic Deficits Over Time

		With neurologic deficit		Without neurologic deficit		Odds ratio (95% CI)	*p* value[a]
Continuous EEG features		N	Median (IQR)	N	Median (IQR)		
Average background voltage, μV[b]	Discharge	60	60 (40, 80)	84	75 (50, 100)	0.91 (0.83, 1.00)	0.06
	6 months	11	40 (30, 40)	131	70 (50, 90)	0.66 (0.48, 0.92)	**0.01**
	12 months	7	40 (30, 40)	134	70 (50, 90)	0.56 (0.34, 0.91)	**0.02***
	24 months	6	35 (30, 40)	132	70 (50, 90)	0.58 (0.35, 0.96)	**0.03***
Dominant frequency, Hz	Discharge	58	2.0 (1.5, 2.5)	84	2.0 (2.0, 3.0)	0.74 (0.50, 1.10)	0.14
	6 months	10	1.5 (1.0, 2.0)	130	2.0 (1.5, 2.5)	0.24 (0.08, 0.66)	**0.01***
	12 months	6	1.3 (1.0, 2.0)	133	2.0 (1.5, 2.5)	0.22 (0.06, 0.80)	**0.02***
	24 months	5	1.0 (1.0, 1.5)	131	2.0 (1.5, 2.5)	0.16 (0.04, 0.69)	**0.01***
Categorical EEG features		N	n (%)	N	n (%)		
Vertex sharp waves	Discharge	60	26 (43.3)	84	31 (36.9)	1.30 (0.67, 2.55)	0.44
	6 months	11	4 (36.4)	131	51 (38.9)	0.94 (0.28, 3.18)	0.92
	12 months	7	2 (28.6)	134	52 (38.8)	0.71 (0.15, 3.31)	0.67
	24 months	6	1 (16.7)	132	53 (40.2)	0.41 (0.06, 2.55)	0.34
Sleep spindles	Discharge	60	35 (58.3)	84	53 (63.1)	0.82 (0.42, 1.61)	0.56
	6 months	11	7 (63.6)	131	80 (61.1)	1.07 (0.31, 3.61)	0.92
	12 months	7	5 (71.4)	134	81 (60.5)	1.44 (0.31, 6.70)	0.64
	24 months	6	5 (83.3)	132	79 (59.9)	2.47 (0.39, 15.51)	0.34
Normal reactivity	Discharge	53	21 (39.6)	78	34 (43.6)	0.85 (0.42, 1.72)	0.66
	6 months	9	3 (33.3)	121	52 (43.0)	0.71 (0.19, 2.74)	0.62
	12 months	6	2 (33.3)	124	53 (42.7)	0.74 (0.15, 3.63)	0.71
	24 months	5	1 (20.0)	122	53 (43.4)	0.43 (0.07, 2.84)	0.38
Asymmetry	Discharge	59	8 (13.6)	86	12 (14.0)	0.98 (0.38, 2.52)	0.97
	6 months	11	5 (45.5)	131	14 (10.7)	6.86 (1.95, 24.17)	**0.003***
	12 months	7	4 (57.1)	134	15 (11.2)	9.91 (2.23, 44.15)	**0.003***
	24 months	6	4 (66.7)	132	15 (11.4)	13.65 (2.66, 69.94)	**0.002***
Variability	Discharge	61	39 (63.9)	84	58 (69.1)	0.80 (0.40, 1.59)	0.52
	6 months	11	6 (54.6)	132	90 (68.2)	0.55 (0.17, 1.83)	0.33
	12 months	7	3 (42.9)	135	92 (68.2)	0.37 (0.09, 1.55)	0.17
	24 months	6	2 (33.3)	133	90 (67.7)	0.27 (0.05, 1.31)	0.10
Epileptiform discharges	Discharge	61	9 (14.8)	87	11 (12.6)	1.20 (0.48, 3.05)	0.70
	6 months	11	5 (45.5)	135	15 (11.1)	6.58 (1.88, 23.02)	**0.003***
	12 months	7	3 (42.9)	138	17 (12.3)	5.40 (1.22, 23.82)	**0.03**
	24 months	6	3 (50.0)	136	16 (11.8)	7.30 (1.52, 35.05)	**0.01***
Electrographic seizures	Discharge	61	5 (8.2)	87	6 (6.9)	1.22 (0.37, 3.99)	0.74
	6 months	11	3 (27.3)	135	8 (5.9)	6.18 (1.49, 25.69)	**0.01***
	12 months	7	3 (42.9)	138	8 (5.8)	11.94 (2.51, 56.81)	**0.002***
	24 months	6	3 (50.0)	136	8 (5.9)	15.12 (2.94, 77.63)	**0.001***



[a]Binary logistic regression using Firth penalized likelihood procedure, adjusted for antiseizure medication use before EEG. [b]Rescaled as μV/10 in logistic regression model. Red indicates significant association between EEG feature and protection or risk of neurologic deficit at each time point before correction for multiplicity. *Significant *p* value after correction for multiple comparisons using Benjamini-Hochberg false discovery rate approach.

associated with long-term neurologic deficits. Thus, the evaluation of postadmission number of seizures may be useful in identifying children at highest risk of neurologic deficits. Prediction of children at highest risk of cognitive impairment is more complex, but this study shows that specific EEG features (average background voltage, dominant rhythm frequency, presence of vertex sharp waves, presence of variability) and seizure number are each independently associated with specific cognitive outcomes. The study findings provide a basis for future studies that evaluate the predictive value of these clinical and EEG features for cognitive impairment. Such studies could potentially identify children at greatest risk of long-term cognitive impairment. Identification of these children, and the development of interventions that can decrease long-term impairment in these children, could substantially decrease the long-term neurocognitive burden of CM.

Previous studies of EEG findings in CM have focused on mortality and neurologic deficit outcomes. Our study findings are largely consistent with these studies which showed

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Table 1 Performance of Clinical and EEG Features on Neurologic Deficits at Discharge and 6-, 12-, and 24-Month Follow-up

	0 mo N = 111		6 mo N = 110		12 mo N = 109		24 mo N = 106	
	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
Blantyre Coma Score <2	51.2	64.3	22.5	98.6	12.8	98.6	13.5	100
No. of seizures >4	85.7	61.5	83.3	95.2	66.7	98.1	66.7	99.0
Avg. background voltage <50 μV	58.3	63.2	36.0	98.8	24.0	100	20.8	100
Dominant rhythm frequency <2.5 Hz	52.2	68.8	11.1	96.2	6.7	98.1	6.8	99.0
Asymmetry	40.9	63.4	19.1	95.3	14.3	97.6	14.3	98.4

Abbreviations: NPV = negative predictive value; PPV = positive predictive value.

associations of lower average and maximal voltages, focal slowing, and a lack of reactivity with an increased likelihood of death.[11] In other studies of EEG in CM, asymmetry and lower voltages were independently associated with an increased mortality risk.[31] Similarly, we found, consistent with other studies, that lower average voltage was associated with neurologic deficits at discharge and/or in follow-up[11,31] but did not find the association of sleep spindles with decreased odds of neurologic sequelae.[31]

EEG features did not provide substantially better negative or positive predictive value for the presence of neurologic deficits 6 months to 2 years after admission for CM than the simple measure of the number of clinical seizures postadmission. In this study, a cut-off threshold of ≥4 seizures during admission provided the greatest predictive value for long-term neurologic deficits. Future studies should determine whether this cutoff is consistent and replicated such that it could be used to identify children at risk for adverse neurologic outcomes.

Neurologic deficits decreased significantly from discharge (41%) to the 6-month follow-up (7.5%). Of the 10 children with deficits at 6 months, 6 still had deficits at 12 months (4.8%) and 5 at 24 months (4.2%). These findings are consistent with previous studies[34] and suggest that most neurologic recovery in children with CM occurs within the first 6 months after acute illness. Foreknowledge of the small subset (4.2%) of CM survivors whose deficits persist for 2 years or more could help to identify those at highest need of early physical therapy or other neurologic rehabilitation.

Poor cognitive outcomes in children with CM younger than 5 years are strongly associated with increased numbers of clinical seizures during the index illness. An increased number of

Table 2 Association of Number of Seizures During Hospitalization and Coma Score With Cognitive Outcomes

		<5 y at cerebral malaria episode			<5 y at cerebral malaria episode, but >5 y at follow-up testing			>5 y at cerebral malaria episode		
Clinical measure	**Cognitive outcome**	**N (obs), N[a]**	**β (95% CI)**	***p* Value**	**N (obs), N[a]**	**β (95% CI)**	***p* Value**	**N (obs), N[a]**	**β (95% CI)**	***p* Value**
No. of seizures	Overall cognition	351 to 115	−0.18 (−0.30 to −0.05)	**0.006**	82 to 61	−0.23 (−0.34 to −0.11)	**<0.001**	129 to 33	−0.27 (−0.93 to 0.40)	0.42
	Attention	361 to 116	−0.09 (−0.16 to −0.02)	**0.009**	83 to 61	−0.24 (−0.35 to −0.13)	**<0.001**	126 to 33	0.07 (−0.35 to 0.49)	0.74
	Memory[b]	362 to 116	−0.02 (−0.06 to 0.01)	0.17	83 to 61	−0.30 (−0.44 to −0.15)	**<0.001**	129 to 33	−0.03 (−0.47 to 0.41)	0.89
Blantyre or Glasgow Coma Score	Overall cognition	351 to 115	0.57 (0.02 to 1.13)	**0.04**	82 to 61	0.24 (−0.33 to 0.80)	0.40	129 to 33	−0.24 (−1.28 to 0.81)	0.65
	Attention	361 to 116	0.12 (−0.20 to 0.45)	0.45	83 to 61	0.62 (0.05 to 1.20)	**0.03**	126 to 33	−0.34 (−0.94 to 0.26)	0.26
	Memory[b]	362 to 116	0.12 (−0.03 to 0.28)	0.12	83 to 61	1.21 (0.53 to 1.89)	**0.001**	129 to 33	−0.10 (−0.83 to 0.64)	0.79

Results from linear mixed-effects model adjusted for age, socioeconomic status, home environment z-score, and antiseizure medication administration.
[a] N (obs), total number of testing visits for all children included in the analysis; N, unique number of children included in the analysis.
[b] Associative memory for children <5 years, working memory for children 5 years or older. Results in bold considered significant with *p* value ≤ 0.05.

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Table 3 Association of EEG Features With Cognitive Outcomes

		<5 y at cerebral malaria episode			<5 y at cerebral malaria episode, but ≥5 y at follow-up testing			≥5 y at cerebral malaria episode		
EEG measure	**Cognitive outcome**	**N (obs), N[a]**	**β (95% CI)**	***p* Value**	**N (obs), N[a]**	**β (95% CI)**	***p* Value**	**N (obs), N[a]**	**β (95% CI)**	***p* Value**
Continuous EEG features										
Average background voltage (log_{10})	Overall cognition	336 to 111	0.57 (−1.17 to 2.31)	0.51	81 to 60	1.35 (−0.38 to 3.08)	0.12	129 to 33	−0.95 (−4.78 to 2.88)	0.62
	Attention	345 to 112	0.66 (−0.26 to 1.59)	0.16	82 to 60	1.66 (−0.13 to 3.45)	0.07	126 to 33	−0.27 (−2.65 to 2.11)	0.82
	Memory[b]	347 to 112	0.54 (0.08 to 1.00)	**0.02***	82 to 60	2.07 (−0.10 to 4.23)	0.06	129 to 33	0.46 (−2.03 to 2.95)	0.71
Dominant frequency	Overall cognition	329 to 109	0.45 (0.04 to 0.86)	**0.03***	80 to 59	0.55 (0.17 to 0.93)	**0.004***	129 to 33	0.37 (−0.32 to 1.06)	0.28
	Attention	338 to 110	0.35 (0.14 to 0.55)	**0.001***	81 to 59	0.43 (0.08 to 0.79)	**0.02***	126 to 33	0.26 (−0.16 to 0.67)	0.22
	Memory[b]	340 to 110	0.21 (0.10 to 0.32)	**<0.001***	81 to 59	0.52 (0.07 to 0.97)	**0.02***	129 to 33	0.34 (−0.10 to 0.78)	0.12
Categorical EEG features										
Vertex sharp waves	Overall cognition	336 to 111	0.59 (−0.08 to 1.27)	0.08	81 to 60	0.69 (−0.09 to 1.46)	0.08	129 to 33	−0.03 (−1.68 to 1.62)	0.97
	Attention	345 to 112	0.28 (−0.10 to 0.65)	0.14	82 to 60	0.83 (0.11 to 1.55)	0.02	126 to 33	0.42 (−0.57 to 1.42)	0.39
	Memory[b]	347 to 112	−0.00 (−0.19 to 0.19)	0.99	82 to 60	0.39 (−0.53 to 1.31)	0.40	129 to 33	0.33 (−0.74 to 1.39)	0.54
Sleep spindles	Overall cognition	336 to 111	0.17 (−0.54 to 0.89)	0.63	81 to 60	−0.12 (−0.91 to 0.68)	0.77	129 to 33	0.94 (−0.65 to 2.53)	0.24
	Attention	345 to 112	0.08 (−0.32 to 0.47)	0.70	82 to 60	0.40 (−0.34 to 1.14)	0.29	126 to 33	0.10 (−0.90 to 1.10)	0.84
	Memory[b]	347 to 112	−0.05 (−0.24 to 0.15)	0.65	82 to 60	−0.31 (−1.22 to 0.61)	0.51	129 to 33	−0.25 (−1.31 to 0.81)	0.64
Normal reactivity	Overall cognition	304 to 101	0.31 (−0.41 to 1.04)	0.39	76 to 57	0.33 (−0.48 to 1.14)	0.42	120 to 30	0.60 (−1.10 to 2.30)	0.47
	Attention	314 to 102	0.15 (−0.25 to 0.54)	0.46	77 to 57	0.80 (0.05 to 1.54)	0.04	117 to 30	0.52 (−0.49 to 1.53)	0.30
	Memory[b]	314 to 102	0.01 (−0.20 to 0.22)	0.90	77 to 57	0.75 (−0.16 to 1.67)	0.11	120 to 30	1.02 (0.08 to 1.96)	0.03
Asymmetry	Overall cognition	337 to 111	−0.59 (−1.58 to 0.39)	0.23	81 to 60	−0.71 (−2.05 to 0.64)	0.30	129 to 33	0.89 (−1.40 to 3.18)	0.43
	Attention	346 to 112	−0.23 (−0.76 to 0.31)	0.40	82 to 60	−1.86 (−3.18 to −0.54)	**0.01***	126 to 33	−1.09 (−2.43 to 0.25)	0.11
	Memory[b]	348 to 112	−0.18 (−0.45 to 0.09)	0.19	82 to 60	−1.36 (−3.00 to 0.28)	0.10	129 to 33	−0.09 (−1.60 to 1.41)	0.90
Variability	Overall cognition	339 to 112	0.26 (−0.44 to 0.95)	0.46	82 to 61	0.84 (0.09 to 1.60)	0.03	129 to 33	0.26 (−1.60 to 2.12)	0.78
	Attention	348 to 113	0.27 (−0.11 to 0.65)	0.16	83 to 61	1.17 (0.52 to 1.83)	**<0.001***	126 to 33	1.08 (0.03 to 2.14)	0.04
	Memory[b]	350 to 113	0.03 (−0.16 to 0.22)	0.78	83 to 61	0.77 (−0.12 to 1.65)	0.09	129 to 33	0.88 (−0.29 to 2.04)	0.13
Epileptiform discharges	Overall cognition	351 to 115	−0.63 (−1.65 to 0.40)	0.23	82 to 61	−1.23 (−2.82 to 0.37)	0.13	129 to 33	−0.95 (−3.15 to 1.24)	0.38

Continued

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Table 3 Association of EEG Features With Cognitive Outcomes *(continued)*

EEG measure	Cognitive outcome	<5 y at cerebral malaria episode			<5 y at cerebral malaria episode, but ≥5 y at follow-up testing			≥5 y at cerebral malaria episode		
		N (obs), N[a]	β (95% CI)	*p* Value	N (obs), N[a]	β (95% CI)	*p* Value	N (obs), N[a]	β (95% CI)	*p* Value
	Attention	360 to 116	−0.57 (−1.12 to −0.02)	**0.04**	83 to 61	−0.65 (−2.34 to 1.05)	0.45	126 to 33	−1.66 (−2.84 to −0.48)	0.01
	Memory[b]	362 to 116	−0.16 (−0.44 to 0.12)	0.26	83 to 61	−0.99 (−3.03 to 1.06)	0.34	129 to 33	−0.92 (−2.32 to 0.48)	0.19
Electrographic seizures	Overall cognition	351 to 115	−0.46 (−1.67 to 0.75)	0.45	82 to 61	−2.21 (−4.19 to −0.22)	0.03	129 to 33	−1.47 (−4.93 to 1.98)	0.39
	Attention	360 to 116	−0.71 (−1.34 to −0.08)	0.03	83 to 61	−2.00 (−3.99 to −0.01)	0.05	126 to 33	−2.13 (−4.08 to −0.18)	0.03
	Memory[b]	362 to 116	−0.11 (−0.44 to 0.22)	0.52	83 to 61	−2.71 (−5.16 to −0.27)	0.03	129 to 33	−1.86 (−4.01 to 0.30)	0.09

Results from linear mixed-effects model adjusted for age, socioeconomic status, home environment z-score, and antiseizure medication before EEG.
[a] N (obs), total number of testing visits for all children included in the analysis; N, unique number of children included in the analysis.
[b] Associative memory for children <5 years, working memory for children 5 years or older.
*Significant *p* value after correction for multiple comparisons using Benjamini-Hochberg false discovery rate approach (6 comparisons for continuous EEG features and 21 comparisons for categorical EEG measures).

seizures are associated with worse long-term outcomes in all domains (overall cognition, attention, and working memory) in children younger than 5 years, but not in children 5 years or older. This suggests that the immature brain may be more sensitive to secondary injury from uncontrolled seizures. It is known that electrographic status epilepticus is associated with mortality in critically ill children without malaria[35,36] and can compound neurologic injury.[37-40] It is possible that identification of electrographic status epilepticus, early treatment of electrographic seizures, and aggressive reductions in seizure burden may be neuroprotective for long-term neurologic or cognitive sequelae, but this is currently unproven.

Admission EEG features were associated with cognitive outcomes in children younger than 5 years. Lower average EEG voltage was associated with significantly worse associative memory scores, and lower dominant frequency was associated with worse scores in all cognitive domains (cognitive ability, attention, and associative memory). These findings are consistent with findings in other comatose states related to diffuse brain injury (e.g., neonatal hypoxic-ischemic encephalopathy, cardiac arrest), in which low-voltage EEG is associated with unfavorable long-term neurocognitive or neurodevelopmental outcomes.[41,42]

In children younger than 5 years at the time of CM but 5 years or older at testing, the presence of state variability on EEG was associated with higher attention scores, while the presence of vertex waves was associated with better overall cognitive outcomes. In nonmalarial critical illness, the lack of normal sleep architecture or changes in state are associated with increased mortality in critically ill comatose patients both without[43] and with[44] acute cerebral injury. In our study, increased mortality risk was associated with attenuated voltage and lack of reactivity. The presence of vertex waves, a normal sleep element, and state variability were associated with improved long-term neurocognitive outcomes. Similarly, the presence of state variability and sleep architecture are biomarkers of the severity of acute cerebral injury due to CM. However, sleep may have a neuroprotective effect during CM leading to better long-term outcomes. It is possible that sleep states allow clearance of excitotoxic signal molecules from active neurons and neurotoxic substances from neuronal damage.[45,46]

Limitations of our study include the short (30-minute) duration of EEG recordings, which may fail to capture more transient EEG features. Continuous EEG monitoring, unavailable at our research site, would likely improve the sensitivity and specificity of clinical seizure detection, detect subclinical seizures, and quantify seizure burden.[47,48] We did not include EEG or neuropsychological follow-up for children who were admitted in coma but recovered consciousness before EEG acquisition. EEG studies were interpreted by a pediatric neurologist with experience in children with CM. Although this avoids concerns with inter-rater reliability, it is possible that the use of multiple EEG interpreters with

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Table 4 Independent Association in Multivariable Analysis of Clinical and EEG Features With Cognitive Outcomes

	Overall cognition β (95% CI)	*p* Value	Attention β (95% CI)	*p* Value	Associative memory β (95% CI)	*p* Value
Children <5 y at cerebral malaria episode						
No. of clinical seizures	−0.18 (−0.34 to −0.02)	**0.03**	−0.06 (−0.14 to 0.01)	0.10	−0.02 (−0.06 to 0.03)	0.49
Average background voltage (log_{10})	0.34 (−1.59 to 2.26)	0.73	0.53 (−0.38 to 1.44)	0.25	0.59 (0.07 to 1.11)	**0.03**
Dominant frequency	0.43 (−0.02 to 0.88)	0.06	0.29 (0.07 to 0.51)	**0.01**	0.23 (0.10 to 0.36)	**0.001**
Vertex sharp waves	0.75 (0.01 to 1.50)	**0.05**	0.33 (−0.03 to 0.69)	0.07	0.03 (−0.18 to 0.24)	0.78
Normal reactivity	0.33 (−0.55 to 1.21)	0.46	−0.04 (−0.48 to 0.39)	0.85	0.01 (−0.24 to 0.26)	0.96
Asymmetry	−0.04 (−1.30 to 1.22)	0.95	−0.37 (−0.99 to 0.25)	0.24	−0.33 (−0.68 to 0.03)	0.07
Variability	−0.23 (−1.14 to 0.68)	0.62	0.11 (−0.34 to 0.56)	0.62	−0.09 (−0.34 to 0.17)	0.49
Children <5 y at cerebral malaria episode but ≥5 y at follow-up testing						
No. of clinical seizures	−0.14 (−0.27 to −0.01)	**0.03**	−0.14 (−0.25 to −0.02)	**0.02**	−0.17 (−0.33 to −0.01)	**0.04**
Average background voltage (log_{10})	0.88 (−0.69 to 2.46)	0.26	0.84 (−0.65 to 2.33)	0.26	1.24 (−0.87 to 3.34)	0.24
Dominant frequency	0.47 (0.08 to 0.86)	**0.02**	0.28 (−0.08 to 0.64)	0.13	0.39 (−0.13 to 0.91)	0.14
Vertex sharp waves	0.81 (0.10 to 1.52)	**0.03**	0.52 (−0.15 to 1.19)	0.12	0.19 (−0.75 to 1.14)	0.68
Normal reactivity	−0.28 (−1.11 to 0.55)	0.50	0.14 (−0.63 to 0.92)	0.71	0.63 (−0.47 to 1.73)	0.26
Asymmetry	0.18 (−1.11 to 1.48)	0.78	−1.09 (−2.32 to 0.14)	0.08	−0.83 (−2.56 to 0.90)	0.34
Variability	—	—	0.86 (0.03 to 1.68)	**0.04**	0.22 (−0.95 to 1.39)	0.71

Multivariable linear mixed-effects models adjusted for age, socioeconomic status, home environment z-score, and antiseizure medication before EEG. Results in bold considered signficant with *p* value ≤ 0.05.

adjudicated reads may have changed our study's findings. Study strengths included rigorous inclusion and exclusion criteria; detailed and appropriate clinical, neurologic, and cognitive evaluation; outstanding follow-up through 2 years after the CM episode (>95%); and high quality of the EEG testing, with interpretation by a board-certified neurologist.

Most EEG use in Africa is in large referral hospitals, such as the one where our study was performed. For EEG to be useful clinically, trained technologists, equipment, and interpreters must all be available. If EEG equipment and personnel are available, EEG acquisition and interpretation may provide a benefit to children with CM by identifying electrographic-only seizures, facilitating early treatment. In the short-term, the benefit of additional EEG testing is likely to be limited to the few African centers with the equipment, trained technicians, and pediatric neurologist to interpret the EEG. Continued EEG studies in children with CM will nonetheless be important to better define brain physiology during this disease and to evaluate predictive value of study findings for long-term neurologic deficits and cognitive impairment. As costs of EEG equipment decrease and the workforce of technicians and pediatric neurologists in Africa increases, cost-benefit analysis of EEG testing for identification of at-risk children with CM should be performed.

In summary, this study shows that in children with CM, the number of postadmission seizures and specific EEG features on admission are independently associated with long-term cognitive outcomes, while seizure number alone, an easily assessable clinical parameter, is strongly associated with long-term neurologic deficits. Future studies should evaluate the predictive value of these findings to determine whether they can be useful in identification of children who survive CM who are at the highest risk of neurologic deficits or cognitive impairment and allow for evaluation of early interventions, once developed, to prevent or decrease the severity of these complications.

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Appendix Authors

Name	Location	Contribution
Daniel J. Clark, MD, PhD	Division of Neurology, Nationwide Children's Hospital, Columbus, OH	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Caitlin Bond, MPH	Ryan White Center for Pediatric Infectious Diseases & Global Health, Indiana University School of Medicine, Indianapolis, IN	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Alexander Andrews, MD	Department of Pediatrics, MedStar Georgetown University Hospital, Washington, DC	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Daniel J. Muller, MPhil	The George Washington University School of Medicine and Health Sciences, Washington, DC	Drafting/revision of the manuscript for content, including medical writing for content
Angela Sarkisian, BS	The George Washington University School of Medicine and Health Sciences, Washington, DC	Drafting/revision of the manuscript for content, including medical writing for content
Robert O. Opoka, MMED, PhD	Department of Paediatrics and Child Health, Makerere University College of Health Sciences, Kampala, Uganda	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Richard Idro, MBChB, MMED, PhD	Department of Paediatrics and Child Health, Makerere University College of Health Sciences, Kampala, Uganda	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Paul Bangirana, PhD	Department of Psychiatry, Makerere University College of Health Sciences, Kampala, Uganda	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Andy Witten, MD	Department of Neurosurgery, Indiana University School of Medicine, Indianapolis, IN	Analysis or interpretation of data
Nicholas J. Sausen, MD	Department of Pediatrics, Division of Emergency Medicine, University of Minnesota, Minneapolis, MN	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Gretchen L. Birbeck, MD, MPH, DTMH	Department of Neurology, University of Rochester, Rochester, NY; University of Zambia, School of Medicine, Lusaka, Zambia; University Teaching Hospitals Children's Hospital, Lusaka, Zambia	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Chandy C. John, MD, MS	Ryan White Center for Pediatric Infectious Diseases & Global Health, Indiana University School of Medicine, Indianapolis, IN	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Douglas G. Postels, MD, MS	The George Washington University School of Medicine and Health Sciences, Washington, DC; Children's National Medical Center, Washington, DC; Blantyre Malaria Project, Kamuzu University of Health Sciences, Blantyre, Malawi	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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