Published in final edited form as:
Trop Med Int Health. 2011 March ; 16(3): 263–271. doi:10.1111/j.1365-3156.2010.02704.x.

Developmental outcomes in Malawian children with retinopathy-positive cerebral malaria

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Summary

OBJECTIVE—To assess children with retinopathy-positive cerebral malaria (CM) for neurocognitive sequelae.

METHODS—Participants were selected from an ongoing exposure–control study. Eighty-three Malawian children averaging 4.4 years of age and diagnosed with retinopathy-positive CM were compared to 95 controls. Each child was classified as delayed or not using age-based norms for the Malawi Developmental Assessment Tool (MDAT) for developmental delay on the total scale and for the domains of gross motor, fine motor, language and social skills. Groups were also compared on the Achenbach Child Behaviour Checklist (CBCL) (1.5–5 years).

RESULTS—Children with retinopathy-positive CM were delayed, relative to the comparison group, on MDAT total development ($P = 0.028$; odds ratio or OR = 2.13), with the greatest effects on language development ($P = 0.003$; OR = 4.93). The two groups did not differ significantly on the Achenbach CBCL internalizing and externalizing symptoms total scores. Stepwise regression demonstrated that coma duration, seizures while in hospital, platelet count and lactate level on admission were predictive of assessment outcomes for the children with retinopathy-positive CM.

CONCLUSIONS—Children who suffer retinopathy-positive CM at preschool age are at greater risk of developmental delay, particularly with respect to language development. This confirms previous retrospective study findings with school-age children evaluated years after acute illness. The MDAT and the Achenbach CBCL proved sensitive to clinical indicators of severity of malarial illness.

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The authors have no conflicts of interest.

Keywords

malaria; retinopathy; child development; language; motor function; social skills; brain; Malawi; Malawian developmental assessment tasks; Achenbach child behaviour checklist; Socioeconomic status; Africa

Introduction

The malaria parasite *Plasmodium falciparum* causes 500 million clinical episodes of malaria occurring globally each year. More than 90% of these cases occur in Africa, mostly among children. A small proportion of these infections will progress to severe and complicated malaria, resulting in the death of 1 million children 5 years or younger annually in sub-Saharan Africa (Snow *et al.* 2005). Cerebral malaria (CM), a form of severe and complicated malaria, is a clinical syndrome comprised of altered consciousness (Blantyre Coma Score ≤ 2), *P. falciparum* parasitaemia and no other obvious cause of coma (Molyneux 1990).

Prospective studies of school-age children (>5 years) have demonstrated that attention and working memory deficits persist in one of four children with CM 2 years after the illness (Boivin *et al.* 2007; John *et al.* 2008a). Others have noted similar impairment rates, especially with respect to language and memory (Carter *et al.* 2005a,b). Given the incidence of CM and prevalence of neurocognitive impairment in CM survivors, the overall burden of brain injury from malaria is immense, numbering in the hundreds of thousands of African children each year (Holding & Kitsao-Wekulo 2004). Despite the fact that in sub-Sahara Africa children <5 years of age are at greatest risk of severe malaria, prospective studies of the developmental and neurocognitive effects of CM on this age group have not been published.

Another limitation of prior attempts to evaluate the developmental and neurocognitive effects of *P. falciparum* paediatric CM is that malaria-specific retinopathy has not been used to confirm the diagnosis. One in four children with *P. falciparum* parasitaemia who satisfy the standard clinical case definition of CM may have non-malarial etiologies for coma and seizure (Taylor *et al.* 2004). Using malaria retinopathy significantly improves diagnostic accuracy over standard clinical case definition, with 95% sensitivity and 90% specificity using autopsy findings as the gold standard (Beare *et al.* 2006; Birbeck *et al.* 2009).

Finally, prior research evaluating the neurocognitive sequelae of paediatric CM did not include a psychiatric or psychosocial assessment, despite reports that children surviving CM can display persisting behavioural problems (Birbeck *et al.* 2010; Idro *et al.* 2010). Bangirana *et al.* (2009) observed that school-age Ugandan CM survivors exhibited a high level of Achenbach Child Behaviour Checklist (CBCL) internalizing symptoms (depression, anxiety, somatic complaints). These were significantly reduced after a computerized cognitive rehabilitation intervention (Bangirana *et al.* 2009).

The objective of this study was to evaluate the developmental and psychiatric impacts of retinopathy-positive CM (CM-R) in comparison with age-matched preschool children (<6 years) who had not had an episode of CM. The hypotheses tested were (i) that CM-R children have a greater likelihood of developmental delay than the comparison children and (ii) that the CM-R children have a higher level of psychiatric symptoms as measured by the CBCL.

Methods

Study site and population

Queen Elizabeth Central Hospital (QECH) is a tertiary referral centre for a population of 533 000 people in the Blantyre regions and is the primary teaching site for the only medical school in Malawi. The participants in this study were selected from a larger exposure–control study designed to compare rates of epilepsy development in children who survive CM-R (exposed cases) and age-matched, hospitalized children (Birbeck *et al.* 2010). The comparison children included non-comatose children hospitalized with malaria who had severe anaemia and children admitted for anaemia and/or had a simple febrile seizure prior to admission as well as kids with pneumonia, gastroenteritis and dysentery. Children admitted for CM or with a history of CM or other medical history of brain infection (e.g. meningitis, encephalitis) or injury were excluded when compared with children from this study (Birbeck *et al.* 2007, 2009, 2010).

Although the parent study of CM-R epilepsy development was a prospective, *a priori* study, this study was not. Children in this study were recruited during one of the quarterly follow-up neurodisability evaluations for the parent study at QECH. Because the cohorts (CM-R, Comparison) had been enrolled over a 3-year period before this study began, the intervals between CM-R illness and follow-up assessment were not uniform. The CM-R children in this study were assessed 1–40 months after the CM illness (M = 1.43 years, SD = 0.98). Likewise, the comparison children were assessed 1–40 months after their discharge from hospital (M = 1.19 years, SD = 0.78) (Table 1) and only after full recovery from their illness.

We obtained informed written consent from the parent or principal caregiver of each study child. Human subjects protection institutional review board approval for this study was granted by Michigan State University and the College of Medicine for the University of Malawi. The informed consent process and the clinical evaluations were conducted using the local language, Chichewa, by Malawian research nurses fluent in that language.

Malawi Developmental Assessment Tool (MDAT)

The MDAT is a culturally specific tool developed by Gladstone *et al.* (2009) after careful qualitative evaluation of culturally appropriate developmental domains for rural Malawi. The original tool was created by adapting items from Western tools such as the Denver II and the Griffith's (Gladstone *et al.* 2008), but after substantial re-adaptation and in-depth qualitative work, the newer MDAT was created (Gladstone *et al.* 2010). It is standardized with culturally appropriate developmental milestones on 1446 normal rural children from 0 to 6 years in rural Malawi. The MDAT has demonstrated good reliability, construct validity and sensitivity in predicting moderate to severe neurodisability as well as developmental delay in a Malawian population of malnourished children (Gladstone *et al.* 2010).

In this study, the MDAT was administered by two research nurses, well trained in administering the test. The examiners used floor and ceiling methods, whereby for any given developmental domain, it was checked that the child could pass up to seven items in a row before questioning below the developmental age of the child was stopped. Furthermore, once the child failed seven consecutive items, no further items were asked. This is a technique commonly used in developmental screening tests such as the Denver II as well as in comprehensive developmental assessments such as the Griffiths and Bayley. The advantage of this procedure is that it prevents the examiner from prolonging an examination by administering items that are obviously well below or above a child's developmental stage.

The administration of the MDAT usually lasted about 30–45 min. Each child is assessed in a quiet and private evaluation room, following a brief physical exam by the assessment nurses to ensure that the child was not feverish or unwell on that day. Children who were not well were referred to the paediatric outpatient clinic for treatment and scheduled for a different developmental follow-up assessment date. After the MDAT, the principal caregiver completed the CBCL where it was orally administered by a research assistant in the local language of Chichewa. This usually took about 30 min to complete.

Developmental delay on the total MDAT was defined as delay in any one or more of the four developmental domains (Gladstone *et al.* 2010). Delay in any domain was defined as performance below the 90% confidence interval on two or more items, relative to the normative data for children of that age and gender. This typically meant failing at least several items in a given domain for his or her age level.

Child Behaviour Checklist

The preschool version of the CBCL (1.5–5 years) (Achenbach & Rescorla 2000) was translated into the local language independently by three individuals trained in psychology. All three versions were compared by the study team, led by FK and MV, and discrepancies in translation reconciled by a consensus panel of two Malawian research nurses and a psychologist. It was then back-translated to ensure fidelity to the original instrument. The CBCL was administered to the principal caregiver (usually the mother) after MDAT assessment. The total number and type of symptoms from the internalizing domain (e.g. depression, anxiety, withdrawal, somatic complaints) and externalizing domain (e.g. aggressiveness, obstinacy and psychosocial deviance) were recorded for each participant.

Socio-economic status (SES)

The SES questionnaire used in conjunction with the MDAT included a series of questions about parental status and education and occupation, physical quality of home environment (e.g. type of toilet, roof, floor, electricity, water source), material possessions (e.g. mode of transportation, appliances, TV, radio) and food security. These items were used to derive an SES index using methods developed by the World Bank (Filmer & Pritchett 2008).

Physical development

The weight, height and mid-upper-arm circumference of the child were measured before assessment, and these were standardized using the Epi Info Centers for Disease Control & Prevention (CDC) 2000 normative database for physical development (Epi Info CDC 2000).

Statistical methods

The proportion of each group (CM-R, Comparison) with ‘overall delay’ was compared using the Chi-Square test. The two groups were then compared using a binomial logistic regression analysis for the outcome (delayed/normal). Gender, SES and weight-for-age *z* score (WAZ; Epi Info CDC 2000) were controlled for in the binomial regression because of the impact of these factors on total MDAT developmental status.

We also compared the two groups on total quantitative scores for the MDAT domains (gross motor, fine motor, language, social skills) and for the CBCL (internalizing symptoms total, externalizing symptoms total). For these comparisons, we used an analysis of covariance (ANCOVA) with age, gender, SES and WAZ score as the covariates. For these between-group comparisons, the observed power is reported for each factor to reflect the chance of detecting the observed factor effect with the present sample size. All statistical analyses were completed using SPSS 18.0.

Because no Malawi-based norms are available for the CBCL, we did not complete the binomial regression analysis for the CBCL. This comparison is restricted to the total scores for each of the externalizing and internalizing symptoms.

Results

Of 119 from the parent study (Birbeck *et al.* 2010) who were still of preschool age at the start of our study, 83 CM survivors with confirmed malaria retinopathy (42 girls and 41 boys from 1.47 to 6.28 years of age at the time of assessment, median = 4.5 years) were enrolled (70%). Of 233 preschool comparison children, 95 (40.8%) were enrolled (46 girls, 49 boys from 1.52 to 6.10 years of age, median = 4.2). In both groups, children enrolled in this study were of comparable age and gender from their respective cohorts as those children in the parent study who were not enrolled in this study.

The comparison and CM-R groups were comparable on all physical development and descriptive characteristics such as age, measures of weight, height and mid-upper-arm circumference, gender and SES (Table 1). The length of time between discharge from hospital and MDAT/CBCL outcomes assessment (assessment interval) did not differ significantly between the CM-R and comparison groups (Table 1). For the CM-R children, assessment interval did not correlate significantly with any of the MDAT or CBCL outcome measures. After controlling for age, gender, WAZ and SES in regression analysis, the variable of assessment interval had a *P*-value of 0.40 for MDAT Gross Motor as the outcome, 0.61 for MDAT Fine Motor, 0.25 for MDAT Language, 0.25 for MDAT Social Skills, 0.09 for CBCL Internalizing Symptoms and 0.05 for CBCL Externalizing Symptoms.

MDAT-determined developmental delay

A significantly higher percentage of CM-R children were delayed in at least one domain of the MDAT assessment (CM-R: 37.3%, comparison: 21.1%; $P = 0.016$) (Table 2). This was substantiated using a logistic regression analysis controlling for gender, SES and WAZ; the odds ratio (OR) was 2.13 ($P = 0.028$).

For the MDAT language domain, there was a significantly greater likelihood of developmental delay among the CM-R children (CM-R: 21.7%, comparison: 5.3%; $P = 0.001$), again supported by a similar logistic regression analysis, the OR was 4.93 ($P = 0.003$). The between-group difference on MDAT language delay remained significant when applying a Bonferroni adjustment for the number of simultaneous between-group comparisons (four) in the analyses.

For MDAT gross motor function, there was a greater likelihood of developmental delay among the CM-R children (CM-R: 14.5%, comparison: 5.3%; $P = 0.037$), but the difference was no longer statistically significant once gender, SES and WAZ were included as control variables in the logistic regression ($P = 0.056$). For MDAT fine motor function, there was a greater likelihood of developmental delay among the CM-R children, but the difference was not significant (CM-R: 19.3%, comparison: 10.5%; $P = 0.099$). Likewise, for MDAT social skills, there was a greater likelihood of developmental delay among the CM-R children, but the difference was not significant (CM-R: 19.3%, comparison: 13.7%; $P = 0.313$).

MDAT scores

Comparisons of the total MDAT performance scores were consistent with the delayed/not-delayed binary findings after controlling for age, gender, SES and WAZ within an analysis of covariance (ANCOVA) comparing the two groups (CM-R, comparison) (Table 3). The CM-R group scored significantly lower than the comparison group on MDAT total score (*P* =

0.014), gross motor function ($P = 0.007$), fine motor ($P = 0.029$) and language ($P = 0.022$). There were no significant differences between the two groups on social skills ($P = 0.33$).

Achenbach CBCL

The CM-R group had more symptoms on the internalizing (e.g. depression, anxiety, withdrawal, somatic complaints) and externalizing domains (e.g. aggression, misconduct, psychosocial deviance). However, the differences between the CM-R and comparison groups were not statistically significant (Table 4).

Clinical features and MDAT/CBCL outcomes

We can use clinical indicators of the severity of malarial illness to help gauge the utility of the MDAT and CBCL assessments in assessing the developmental impact of this disease. After age, gender, WAZ and SES were forced into the model, a stepwise regression analysis evaluated the predictive value of a number of factors, which might play a role in neurological outcome of children with CM. These included HIV status, history of febrile seizures before the index CM illness, occurrence of seizures at or during hospitalization for CM, epilepsy development after recovery from CM and clinical laboratory features assessed at the time of admission (haematocrit, platelet count and whole blood lactate concentration). For the CM-R children, platelet and lactate levels at hospital admission were significantly predictive of MDAT total score, fine motor and language (Table 5). They were also predictive of CBCL externalizing symptoms. Coma duration following hospitalization was predictive of MDAT gross motor and social skills, while the occurrence of seizures during hospitalization and platelet levels were predictive of CBCL internalizing symptoms.

Discussion

Cerebral malaria confirmed with retinopathy children were more likely to be delayed on MDAT total development with the greatest effects on language development. However, there were no significant differences between the CM-R and comparison groups on the CBCL. Our MDAT findings extend those of the parent study in which retinopathy-positive CM is a risk factor for several adverse neurological outcomes, including epilepsy, disruptive behavioural disorders and neurodisabilities characterized by motor, sensory or language deficits (Birbeck *et al.* 2010). In the Birbeck *et al.* study, most of the sequelae were delayed in presentation and hence were not evident at the time of discharge from the hospital after the initial illness.

The present findings also confirm previous retrospective study findings with school-age children evaluated years after acute illness (Carter *et al.* 2005a,b). Our patient group is younger than those previously studied, extending previous neuropsychological study findings with CM (Kihara *et al.* 2006) for the first time to younger survivors. Our study also extends these findings for the first time to CM children whose diagnosis was confirmed by positive malarial-specific retinopathy during acute illness.

A stepwise regression model demonstrated that coma duration, seizures while in hospital, and platelet count and lactate level on admission were predictive of MDAT and CBCL outcomes for the CM-R children. The fact that clinical factors indicative of severity of CM illness (WHO, 2000) were predictive of MDAT and CBCL outcomes is further evidence of the sensitivity of these instruments to the developmental effects of the index illness in younger children.

The persistent attention and memory problems observed in CM children may be foundational to the long-term language development impairment observed in the severe malaria survivors described by Carter *et al.* (Boivin & Giordani 2009; Carter *et al.* 2005a,b;

Kihara *et al.* 2006). In fact, a recent study from the Kenyan coast showed that impaired recall and recognition memory was associated with the encephalopathy of severe malaria in school-age children (Kihara *et al.* 2009). The authors concluded that hippocampal effects from CM possibly disrupted language development in their sample of children.

The CM-R and comparison children in this study were drawn from a large exposure/control study in which participants were monitored quarterly for signs of epilepsy and neurodisability (Birbeck *et al.* 2010). In the parent study, 42 of the 132 CM-R children (32%) had adverse neurological outcomes when examined quarterly following their illness. Of these 42 children with neurodisabilities, 12/42 (28.6%) had spastic quadriparesis usually accompanied by language regression and/or cortical blindness; 12/42 (28.6%) had isolated language regression or delayed speech; and 6/42 (14.3%) had motor and language regression or delay. The remaining children had other neuromotor disabilities not involving language. Depth of coma (Blantyre coma score <2) and higher temperature at admission were significantly predictive of behavioural neurodisabilities among these children. Our present study extends these findings by providing a more comprehensive developmental and psychiatric assessment of the effects of retinopathy-positive CM in preschool age children with a subgroup of the parent study.

A subset of participants in the larger exposure/control epilepsy parent study was evaluated with computerized axial tomography (CT) scan if they had persisting signs of neurodisability. Some of these children had focal and multifocal lobar atrophy on CT that co-localized to regions of focal seizures during acute CM (Potchen *et al.* 2009). Clinical and subclinical brain damage of this sort from CM likely contributed to the high prevalence of emergent neuromotor and seizure disorders seen in the CM-R survivors in the parent study (Birbeck *et al.* 2010). This type of brain injury from CM may have also have been responsible for the significantly greater risk of gross motor developmental delay for the CM-R group than in controls in our study.

We did not formally assess hearing as part of this study, but in the larger study, caregivers of several of the children reported language difficulties with associated hearing loss. Hearing loss is known to be an occasional persisting neurological symptom of CM (Idro *et al.* 2007) and may have contributed to the developmental delays identified by the MDAT, particularly language delays.

Another possible limitation of the present study was that the time interval varied between the index illness and the MDAT and CBCL follow-up assessment. However, prior retrospective studies of the neurocognitive effects of CM had varying and long intervals between illness and follow-up assessment (Boivin 2002; Dugbartey *et al.* 1998; Holding *et al.* 1999), up to 9 years in some cases (Carter *et al.* 2005a,b). Furthermore, the illness/assessment interval did not differ between the exposure and comparison groups and was not statistically related to the MDAT or CBCL outcomes for the CM-R group.

Eight of the CM-R children in this study had been diagnosed with epilepsy after their index illness, and three of the eight were on phenobarbitone at the time of their MDAT assessments. However, none of the children with epilepsy had MDAT or CBCL subscale scores identified as outliers using the SPSS box-plot graphing program. It should also be noted that neither epilepsy nor HIV status for the CM-R children proved significant in the final stepwise regression model predicting MDAT and CBCL outcomes.

A prospective neurocognitive longitudinal follow-up of CM survivors throughout childhood would provide a better understanding of how the developmental trajectory is related to specific immunological (John *et al.* 2008b) and neurological markers of severity of CM illness during the acute phase (John *et al.* 2008b,c). Such work may lead to new combination

therapies during illness and rehabilitation intervention during recovery, such as the use of neuroprotective agents during acute illness (Birbeck *et al.* 2010). New rehabilitative neurocognitive and behavioural interventions could also enhance the long-term developmental prospects for these children (Bangirana *et al.* 2006, 2009).

Abbreviations

ANCOVA	analysis of covariance
CBCL	Child Behaviour Checklist
CDC	Centers for Disease Control & Prevention
CM	cerebral malaria
CM-R	cerebral malaria confirmed with retinopathy
CNS	central nervous system
CT	computerized axial tomography
MDAT	Malawi Developmental Assessment Tool
P. falciparum	*Plasmodium falciparum*
QECH	Queen Elizabeth Central Hospital
SES	socio-economic status
WAZ	weight-for-age *z* score

Acknowledgments

Study nurses Theresa Nnensa and Chimwemwe Masiye were responsible for obtaining informed consent, carrying out developmental assessments of our study children and assisting with data entry; their efforts are greatly appreciated. Grace Boivin participated in the initial organization of the study on site, and her efforts as a volunteer are also appreciated. Funding was provided by the Michigan State University Department of Neurology and an Office of the Vice President of Research and Graduate Studies award.

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Table 1

Comparison of control and cerebral malaria retinopathy (CM-R) preschool age groups on demographic characteristics

Characteristics	Comparison *N* = 95 M (SD)	CM-R *N* = 83 M (SD)	*P*[*]
Gender, female *N* (%)	46 (48.4)	42 (50.6)	0.77[†]
Age in years	4.05 (1.3)	4.36 (1.2)	0.09
Weight in kgs	14.3 (2.4)	14.8 (2.3)	0.16
Weight-for-Age *z* score[‡]	−1.10 (1.51)	−1.04 (1.05)	0.78
Height in cm	94.0 (9.3)	96.2 (9.6)	0.15
Height-for-age *z* score	−1.59 (1.41)	−1.56 (1.28)	0.91
Mid-upper-arm circumference (MUAC) in cm	15.2 (1.2)	15.3 (1.0)	0.42
MUAC for height *z* score	−1.06 (0.92)	−1.04 (0.81)	0.85
Socio-economic status score	7.5 (2.0)	7.1 (2.2)	0.28
Interval: hospitalization to assessment (years)	1.19 (0.78)	1.43 (0.98)	0.07
Blood haematocrit at admission (%)	18.5 (5.5)		
Serum lactate at admission (absolute)	6.6 (4.1)		
Blood platelet counts at admission (μl)	89529 (87058)		
Coma duration at admission (h)	40.5 (33.9)		
HIV status, positive *N*/total *N* (%)	10/71 (12.0)		
History of seizures prior to illness	21/83 (25.3)		
Seizures during hospitalization	42/83 (50.6)		
Epilepsy at follow-up after illness	8/81 (9.6)		

[*] Probability based on Student *t*-test for two independent samples, two-tailed test.

[†] Probability based on Chi-Square test.

[‡] *z* scores based on 2000 CDC normative anthropometric measures available in Epi Info. The mean (M) and standard deviation (SD) are presented for each group, along with a statistical probability value (*P*) for the difference between them. Descriptive clinical information for the CM-R group is also presented and included in a stepwise regression analysis for the Malawi Developmental Assessment Tool and Child Behaviour Checklist outcomes considered in Table 5.

Table 2

Frequency of developmental delay for comparison children and cerebral malaria retinopathy (CM-R) based on age-based normative data charts for the Malawi Developmental Assessment Tool (MDAT)

MDAT domain*	Comparison *N* = 95 *N* (%)	CM-R *N* = 83 *N* (%)	*P**	Comparison *vs.* CM-R†	Adjusted *P*‡
Gross motor	5 (5.3)	12 (14.5)	**0.037**	OR 2.91 (CI 0.97 – 8.71)	0.056
Fine motor and visual coordination	10 (10.5)	16 (19.3)	0.099	OR 1.92 (CI 0.81 – 4.56)	0.138
Language	5 (5.3)	18 (21.7)	**0.001**	OR 4.93 (CI 1.74 – 14.01)	**0.003**
Social skills	13 (1 3.7)	16 (19.3)	0.313	OR 1.42 (CI 0.63 – 3.21)	0.403
MDAT total development	20 (21.1)	31 (37.3)	**0.016**	OR 2.13 (CI 1.09 – 4.19)	**0.028**

**P*-value based on Chi-Square test. Significant *P*-values are in bold.

†Odds ratio (OR) and 95% confidence intervals (CI) are presented for binomial logistic analysis. Covariates are gender, socio-economic status and weight-for-age *z* score (Epi Info CDC 2000).

‡*P*-values for binomial logistic analysis and statistically significant values are in bold.

Table 3

This table includes the Malawi Developmental Assessment Tool (MDAT) unadjusted mean (M) and standard deviation (SD) for the comparison and cerebral malaria with retinopathy (CM-R) groups. Also included are the adjusted means (M_{adj}) and standard errors (SE_{adj}), the adjusted between-group effect size, between-group *P*-value and observed power for the ANCOVA between-group comparison. The covariates consist of age, gender, socio-economic status score and weight-for-age *z* score (Epi Info CDC 2000). Statically significant *P*-values are in bold

MDAT global scales raw score totals	**Comparison M (SD) M_{adj} (SE_{adj}) *N* = 95**	**CM-R M (SD) M_{adj} (SE_{adj}) *N* = 83**	**Adjusted group effect M (SE)**	***P*-value for adjusted effect**	**Observed power**
Gross motor	29.2 (5.3)	28.8 (6. 0)	1.57 (0.58)	**0.007**	0.77
	29.7 (0.39)	28.1 (0.42)			
Fine motor and visual coordination	28.7 (4.9)	28.7 (6.5)	1.21 (0.55)	**0.029**	0.59
	29.3 (0.37)	28.0 (0.40)			
Language	27.1 (6.6)	27.0 (7.6)	1.67 (0.73)	**0.022**	0.63
	27.0 (0.49)	26.2 (0.53)			
Social skills	29.4 (4.0)	29.8 (5. 7)	0.55 (0.56)	0.33	0.17
	29.8 (0.38)	29.3 (0.40)			
MDAT total score	114.4 (19.3)	114.2 (24.0)	5.00 (2.02)	**0.014**	0.69
	116.6 (1.37)	111.6 (1.47)			

Table 4

This table includes the Achenbach Child Behaviour Checklist (CBCL) internalizing symptoms total and externalizing symptoms total mean scores (M) and standard deviations (SD) for the comparison and cerebral malaria with retinopathy (CM-R) groups. Also included are the adjusted means (M_{adj}) and standard errors (SE_{adj}), the adjusted between-group effect size, between-group *P*-value and observed power for the ANCOVA between-group comparison. The covariates consist of age, gender, socio-economic status score and weight-for-age *z* score (Epi Info CDC 2000).

CBCL symptoms total	Comparison M (SD) M_{adj} (SE_{adj}) *N* = 95	CM-R M (SD) M_{adj} (SE_{adj}) *N* = 83	Adjusted group M (SE)	*P*-value for adjusted effect	Observed power
Internalizing symptoms	8.3 (7.5)	10.0 (8.5)	1.8 (1.23)	0.15	0.30
	8.2 (0.83)	10.0 (0.89)			
Externalizing symptoms	10.7 (7.4)	11.6 (8.7)	1.1 (1.23)	0.38	0.14
	10.6 (0.83)	11.7 (0.89)			

Table 5

This table is an additive stepwise regression model, which begins by including the covariates from Tables 3 and 4 (age, gender, socio-economic status (SES) score and weight-for-age *z* score (WAZ: Epi Info CDC 2000). These are followed by the cerebral malaria with positive retinopathy (CM-R) clinical measures of HIV status (positive, negative), a reported history of seizures prior to CM illness (History seizures: yes, no), occurrence of observed seizures at admission or during hospitalization (Seizures in hospital: yes, no), confirmed epilepsy 1 year after illness (Epilepsy after illness: yes, no), duration of coma following admission (h), blood haematocrit level at admission (%), serum platelet counts at admission (μl) and serum lactate level at admission (absolute). The predicted outcome measures are the Malawi Developmental Assessment Tool (MDAT) domain scores (Gross Motor, Fine Motor, Language, Social Skills), MDAT total score and Child Behaviour Checklist (CBCL) Internalizing and Externalizing Symptoms total. The stepwise regression stops when all remaining variables have *P*-values >0.15. Empty cells indicate that the enter *P*-value was >0.15. Only the CM-R group is included in this table. Total percentage of explained variance for that outcome measure (R^2) is in the bottom row of the table

Clinical factor	*N*	MDAT gross motor	MDAT fine motor	MDAT language	MDAT social skills	MDAT total score	CBCL internalizing symptoms	CBCL externalizing symptoms
Age (years)	83	0.000	0.000	0.000	0.000	0.000	0.598	0.711
Gender	83	0.624	0.495	0.848	0.881	0.873	0.782	0.490
WAZ	83	0.004	0.049	0.145	0.002	0.015	0.050	0.575
SES	83	0.600	0.173	0.901	0.456	0.256	0.251	0.685
HIV status	71							
History of seizures	83							
Seizures in hospital	83						0.037	
Epilepsy after illness	79							
Coma duration	79	0.001			0.085			
haematocrit	76							
Blood platelets	68		0.007	0.066		0.010	0.127	0.088
Lactate	76		0.002	0.001		0.002		0.114
R^2		67.6%	64.6%	54.5%	47.2%	66.8%	21.5%	17.0%