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Neurocognitive domains affected by cerebral malaria and severe malarial anemia in children

Paul Bangirana[a], **Robert O. Opoka**[b], **Michael J. Boivin**[c], **Richard Idro**[b], **James S. Hodges**[d], and **Chandy C. John**[e]

[a]Department of Psychiatry, Makerere University College of Health Sciences, Kampala, Uganda [b]Department of Paediatrics and Child Health, Makerere University College of Health Sciences, Kampala, Uganda [c]Department of Psychiatry, Michigan State University, East Lansing, Michigan [d]Division of Biostatistics, University of Minnesota School of Public Health, Minneapolis, Minnesota [e]Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota

Abstract

This study assessed the effects of cerebral malaria (CM) and severe malarial anemia (SMA) on individual neurocognitive domains. Eighty children with CM, 86 with SMA, and 61 community children (CC) were assessed for gross motor skills, fine motor skills, visual reception, receptive language, and expressive language a week after discharge (CM or SMA) or at enrolment (CC), and 6 and 12 months later. At 12-months follow-up, children with CM had significantly lower scores than CC for all outcomes. Children with SMA had significantly lower scores than CC for visual reception, receptive language, and expressive language, and scores that were lower but did not reach significance for gross and fine motor skills. Children with CM had significantly lower scores than children with SMA for fine motor skills. Children with SMA and CM have long-term impairment in multiple neurocognitive domains. Fine motor skills may be affected more profoundly in CM than SMA.

Keywords

cerebral malaria; severe malarial anemia; neurocognitive deficits

1. Introduction

Cerebral malaria (CM) and other forms of malaria with neurological involvement are among the main causes of neurodisability in children in sub-Saharan Africa (Idro et al., 2010b). Malaria with neurological involvement mainly affects attention, speech and language,

Corresponding author: Paul Bangirana, PhD, Department of Psychiatry, Makerere University, Box 7072, Kampala, Uganda. Phone: +256-772-673831, pbangirana@yahoo.com.

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memory, executive functions, and visual spatial skills (Carter et al., 2005, John et al., 2008a, Kihara et al., 2006). These deficits have been identified in the short term and in the long term as late as nine years after the illness (Carter et al., 2005, Boivin et al., 2007). Clinical and laboratory features of severe malaria associated with these deficits include coma, seizures, elevated tumour necrosis factor alpha (TNF), and hypoglycaemia (Bangirana et al., 2014, Boivin et al., 2007, Idro et al., 2006, John et al., 2008b). Some of these risk factors for poor neurocognitive outcome like seizures, coma, and elevated TNF are a consequence of the mechanisms involved in the pathogenesis of CM (e.g. sequestration of infected red blood cells and the inflammatory response) (Idro et al., 2005, Idro et al., 2010b). Neurocognitive testing may thus play a role in understanding the mechanisms of brain injury in severe malaria.

In a recent study by our group, Ugandan children with severe malaria anemia (SMA) having no clinical signs of neurologic disability on admission were also found to have long-term reductions in neurocognitive scores (Bangirana et al., 2014). However, CM's effect on neurocognitive ability was more severe than SMA's compared to community control children; CM was associated with a reduction of neurocognitive ability scores analogous to 13 IQ points, while SMA was associated with a reduction analogous to 8 IQ points. The measure of neurocognitive ability used in this study was a composite score from the Mullen Early Learning Scales (Mullen, 1995), the sum of scores from fine motor, visual reception, and language domains. This single score allows for assessment of overall neurocognitive ability but does not provide information about the individual neurocognitive domains. Also, the Mullen Early Learning Scales test gross motor function, but that is not included in the composite score.

Identifying specific abilities affected by CM and SMA may provide insight into how these diseases affect neurocognition. This information will let researchers and clinicians know which specific abilities to assess in children who survive the diseases. Finally, interventions to improve neurocognitive outcome in survivors will be guided by this information. The present study assessed age-adjusted z-scores of children with CM or SMA, compared to community children. We adjusted for confounders, in each of the five neurocognitive domains of gross motor skills, fine motor skills, visual reception, expressive and receptive language, to determine whether scores in specific areas differed between children with CM or SMA and community children, and if they differed between children with CM and SMA. Based on prior studies, we hypothesized that; a) children with CM and SMA will have poorer neurocognitive ability than the controls, and b) children with CM will have poorer neurocognitive ability outcomes in all the domains than children with SMA.

2. Material and methods

2.1 Study participants

The study was performed at Mulago Hospital, Kampala, Uganda. Full details of the study design, participants, clinical assessment, and neurocognitive assessment have been described elsewhere (Bangirana et al., 2014). Briefly, children with CM, SMA, or community children were enrolled if they were aged 18 months to 4 years. Cerebral malaria was defined as: 1) coma (Blantyre Coma Score [BCS] ≤2); 2) *Plasmodium falciparum* on blood smear; and 3)

no other known cause of coma (e.g., meningitis, prolonged postictal state, or hypoglycemia-associated coma reversed by glucose infusion). Severe malarial anemia was defined as presence of *Plasmodium falciparum* on blood smear in children with a hemoglobin level ≤ 5 g/dL. Children with CM or SMA were managed according to the Ugandan Ministry of Health treatment guidelines current at the time of the study. All children with hemoglobin <5 g/dL (all SMA, 29 CM) received a blood transfusion.

Community children (CC) were recruited from the nuclear family, extended family, or household compound area of children with CM or SMA to control for socioeconomic variables that affect neurocognition (Bangirana et al., 2009b). Eligible CC were aged 18 months to 4 years and currently healthy. Children were enrolled if they met inclusion criteria and did not meet exclusion criteria. Exclusion criteria for all children included: 1) known chronic illness requiring medical care; 2) known developmental delay; or 3) prior history of coma, head trauma, hospitalization for malnutrition, or cerebral palsy. Additional exclusion criteria for children with SMA included: 1) impaired consciousness on physical examination; 2) other clinical evidence of central nervous system disease; or 3) >1 seizure in the past 24 hours prior to admission. Additional exclusion criteria for CC included: 1) illness requiring medical care within the previous 4 weeks or 2) major medical or neurological abnormalities on screening physical examination. Written informed consent was obtained from parents or guardians of study participants. Ethical approval was granted by the Institutional Review Boards for human studies at Makerere University School of Medicine, University of Minnesota, Michigan State University and the Uganda National Council for Science and Technology.

2.2 Clinical and demographic assessment

All children underwent a medical history and physical examination. Nutrition was assessed by height- and weight-for-age z-scores (HAZ and WAZ respectively) using CDC 2000 references (Epi Info v. 3.5.3, CDC, Atlanta GA). The quality of the home environment was measured by age-appropriate versions of the Home Observation for the Measurement of the Environment that assess the parent-child interaction and opportunities for learning available in the home (Caldwell and Bradley, 2001). Socioeconomic status was measured using a previously described scoring system consisting of material possessions, housing quality, and water sources, for which lower scores have been associated with poorer neurocognitive functioning in healthy Ugandan children ≥5 years (Bangirana et al., 2009b).

2.3 Neurocognitive assessment

Children were tested either a week after discharge (CM, SMA) or at enrollment (CC), and then 6 and 12 months after discharge or enrollment. The Mullen Scales of Early Learning were used to measure neurocognitive ability (Mullen, 1995). Summary scores for this study were fine motor, gross motor, visual reception, receptive language, and expressive language. The Fine Motor Scale assesses visual motor ability with items involving visual discrimination and motor control including abilities like writing readiness. Gross Motor measures central body control and mobility in supine, prone, sitting, and fully upright positions. The Visual Reception Scale measures performance in processing visual patterns especially visual discrimination and visual memory. Receptive Language measures a child's

ability to process linguistic input mainly in auditory comprehension and auditory memory. The Expressive Language Scale measures the child's ability to use language productively; it mainly covers speaking ability and language formation (Mullen, 1995). Testing was performed in a quiet room by testers with an undergraduate degree in Psychology blinded to each child's study group (CM, SMA, or CC). Testing was administered in Luganda, the local language, for those who did not understand English. Test instructions were translated to Luganda and back-translated by native Luganda speakers. A video of a testing session was reviewed monthly to ensure testing was done correctly and consistently. Testing was performed by the same tester at all three time-points in 114 (50.2%) of the children. In the pilot phase of the study, inter-rater reliability of the testers ranged from 0.78 to 0.99.

2.4 Statistical analyses

Demographic characteristics were compared using t-tests, Fisher's exact test, and Pearson's χ^2 test for continuous, binary, and other categorical measures, respectively. Age-adjusted z-scores for neurocognitive outcomes were created using the scores of the community children (Boivin et al., 2007, John et al., 2008a). For each outcome, the z-score was computed as (actual score minus average score for child's age) / SD, where “average score for child's age” and “SD” were computed by fitting a mixed linear model to data from all available visits for CC (allowing correlated errors for a child's multiple visits). Z-scores are intended have an average of 0 and standard (SD) equal to one in the reference population (CC); however, when constructed using data from multiple visits, as we did, the reference children will have average z-scores for each visit that are very close to but not exactly zero. Groups were compared according to z-scores using all 3 testing times, analyzed using a mixed linear model, which generalizes repeated measured analysis (again allowing correlated errors for a child's multiple visits). Because CC differed from children with CM or SMA in age, WAZ, HAZ, and child education, groups were compared adjusting for these characteristics (neurocognitive ability z-scores are already adjusted for age). Sample sizes of 60 CC and 80 children in each of the CM and SMA groups were estimated *a priori* to give >80% power (alpha=0.05) to detect a z-score difference of 0.5 between each disease group and CC.

For the CM and SMA groups separately, z-scores for each neurocognitive domain were tested for association with clinical features using Pearson correlation for continuous variables (e.g., hemoglobin) and two-sample t-tests for binary variables (present/absent). To account for multiple testing, $P<0.005$ was considered statistically significant for these tests. Mixed linear models were analyzed using SAS's MIXED procedure (v. 9.3, SAS Institute, Cary NC) with default settings. Adjusted averages are SAS's least-squares means. Other analyses were performed in JMP (Pro v. 10.0, SAS Institute, Cary NC).

3. Results

3.1 Clinical and demographic characteristics

Eighty children with CM, 86 with SMA, and 61 community controls were enrolled and tested at baseline, 6, and 12 months. Children with SMA were younger than those with CM (2.5 vs 2.8, $p = 0.001$) and the CC group (2.5 vs 2.9, $p < 0.0001$). The SMA group also had lower average WAZ than the CC group (-1.7 vs -0.7, $p < 0.0001$) and lower average HAZ

than the CM group (-1.1 vs -0.5, p = 0.04). Fewer children with CM and SMA were in school compared to the CC group (8% vs 23%, p = 0.009 and 2% vs 23%, p < 0.0001 respectively). The groups did not differ in their fractions of children with hemoglobin SS, HIV, or stool helminth infection (Table 1).

3.2 Neurocognitive ability outcomes

Children with CM had lower age adjusted z-scores on all five facets of neurocognitive ability compared to the CC group at 12 months (gross motor, -0.54 vs -0.07, p = 0.04; fine motor, -0.93 vs -0.12, p = 0.0001; visual reception, -0.74 vs -0.11, p = 0.004; receptive language, -0.91 vs -0.06, p = 0.0002 and expressive language, -0.72 vs -0.09, p = 0.0002). When scores for all three time points were considered (i.e., the group main effect), the CM group still had lower scores in all five neurocognitive abilities (p < 0.005 for all). The SMA group had significantly lower scores than the CC group in visual reception (-0.61 vs -0.11, p = 0.02), receptive language (-0.56 vs -0.06, p = 0.03) and expressive language (-0.44 vs -0.09, p = 0.04) at 12 months. Scores for gross motor (-0.43 vs -0.07, p = 0.12) and fine motor (-0.48 vs -012, p = 0.09) skills were lower in children with SMA than in CC, but the differences did not reach statistical significance. The same trends were observed when scores from all three time points were considered, though the difference for gross motor skills reached significance (-0.48 vs -0.08, p=0.05).

For all domains, scores showed similar differences between groups one week after admission and at 6-month and 12-month follow-up (Figure 1); tests of the group-by-visit interaction did not approach significance for any outcome (P ≥ 0.24), indicating that the time trends for children with CC or SMA did not differ from CC. Children with CM had lower average scores than children with SMA for all areas of neurocognitive ability at 12 months, with the difference reaching significance for fine motor skills (-0.93 vs -0.48, p = 0.02). When all three time points were considered, fine motor skills (-0.81 vs -0.41, p= 0.02) and visual reception (-0.89 vs -0.49, p = 0.01) were both significantly lower in the CM group (Table 2).

3.3 Clinical factors associated with neurocognitive outcomes

Clinical features assessed as risk factors for adverse neurocognitive outcomes for children with CM and SMA included hypoglycemia (glucose <2.2 mMol/L), days of fever, use of anti-malarial medications before admission, prior seizure history, prior hospitalization, admission temperature, systolic blood pressure (BP), diastolic BP, hypoxia (pulse oxygen saturation <92%), deep respirations, lactic acidosis (lactic acid level ≥5 mMol/L), hyperparasitemia (>250,000 parasites/μL), hemoglobin level, white blood cell count, platelet count, and presence of bacteremia. For children with CM, additional clinical features included presence and number of seizures before admission, Blantyre coma score, coma duration, abnormal posturing, presence and number of seizures after admission, retinopathy findings, and abnormal neurological examination at discharge or 6- or 12-month follow-up.

Neurologic deficits at 6 months and 12 months, longer coma duration, and presence of seizures after admission were associated with poorer scores in all the five neurocognitive outcomes for children with CM (Table 3). A Blantyre coma score of 1 was also associated

with poorer gross motor skills and visual reception for children with CM. No clinical factors were associated with any neurocognitive outcome for children with SMA.

4. Discussion

This study's aim was to describe the neurocognitive domains affected by CM and SMA and compare the effect of these two conditions on neurocognitive function. Adjusting for age, nutritional status, and schooling, scores were significantly lower in all areas for children with CM compared to CC children. For children with SMA, scores were lower than CC children in all areas but did not reach statistical significance at 12 months for gross and fine motor skills; when all time points were considered, the difference in gross motor skills was significant and the difference in fine motor skills was close (P = 0.07). These results confirmed our hypotheses that children with CM and SMA have poorer neurocognitive ability than the controls and that children with CM have poorer neurocognitive ability outcomes in all the domains than children with SMA. Together with the finding that scores in fine motor skills differed between children with CM and SMA, the results suggest that all neurocognitive domains are affected in CM and SMA, but fine motor skills may be more profoundly affected in CM than in SMA.

Similar neurocognitive effects of CM have been documented in a number of retrospective and prospective cohort studies. In Kenya, Carter et al observed speech and language impairment in children who survived CM up to 9 years earlier (range 20 to 112 months) (Carter et al., 2006). Impairments in speech and language were more common than other developmental outcomes (Carter et al., 2005). Boivin et al also observed that Malawian children who survived CM had lower scores than a control group in gross motor, fine motor, and language and that language impairment was the predominant outcome (Boivin et al., 2011). These children were assessed 1 to 40 months after the illness (mean 1.43 years, SD 0.98).

However, in one study that assessed children 3 months after a bout of malaria with neurological involvement (including children with CM), no effect was observed on visual spatial ability, a measure similar to visual reception in the present study, or in other neurocognitive outcomes (Bangirana et al., 2011). These authors concluded that in children aged 5 to 12 years, at 3 months after the illness, effects on cognition may not be evident compared to assessment at a much later date. Their study also had a heterogeneous sample with milder forms of severe malaria, which may have led to these results. The present study suggests that effects on all neurocognitive domains are seen early in children with CM or SMA who are <5 years old, as lower adjusted z-scores were seen 1 week after admission and persisted at 6 and 12 months (Figure 1).

The greater effect of CM than SMA on fine motor skills suggests that the mechanisms involved in the pathogenesis of CM may involve cerebral structures responsible for motor functions. The fine motor scale used in the study has tasks that primarily assess fine motor planning and control (Mullen, 1995). Areas involved in motor planning and control are the premotor area, supplementary motor area, and basal ganglia (Lehéricy et al., 2006, Mushiake et al., 1991, Tanji and Shima, 1994). Neuroimaging studies in pediatric CM

survivors do not provide conclusive evidence that these motor areas are affected though the basal ganglia has been identified to be the most affected structure in children with retinopathy-positive CM (Potchen et al., 2012). The effect of CM on fine motor skills could also result from damage to the tracts connecting primary motor areas to the association areas rather than damage to specific motor areas.

In our earlier study of these two groups, a Blantyre Coma Scale score of 1, having neurologic deficits at 6 and 12 months, longer coma duration, and number of seizures after admission were associated with poor neurocognitive ability (a summation of fine motor, visual reception, receptive language, and expressive language) (Bangirana et al., 2014). These factors were also associated with neurocognitive outcomes in the present study, and all but Blantyre coma score were associated with worse scores in all 5 areas. None of these clinical features is seen in SMA, so the pathway by which it affects neurocognitive ability must be different. Further still, none of the clinical factors measured was associated with poor neurocognitive ability in the SMA group.

Malaria retinopathy is observed in 60% to 70% of children with CM and in 53% of children with SMA suggesting cerebral involvement (Beare et al., 2004, Essuman et al., 2010). It has been hypothesized that the retinopathy-positive children may have more effects in the brain from malaria while retinopathy-negative children may have pre-existing developmental problems that could compromise their cognition (Birbeck et al., 2010a, Potchen et al., 2012). However, it is not yet clear if retinopathy negative children have coma due to a source other than malaria or if retinopathy negative children may simply present with less sequestration but still have *P. falciparum* as the causative agent of their coma. Though degree of malaria retinopathy is associated with persistent neurocognitive outcomes in children (Boivin et al., 2014), we did not see any neurocognitive differences between retinopathy-positive and -negative groups in the present study in the CM group (data not shown). Malaria retinopathy was not measured in the children with SMA, so no conclusions can be drawn about its contribution to the neurocognitive deficits in SMA. At present, the pathogenesis of neurocognitive deficits in SMA is not clear.

Children surviving severe malaria develop specific neurodisabilities at different time points with motor, sensory, and language problems seen much earlier, then behavioral problems emerge in the midterm while epilepsy appears much later (Birbeck et al., 2010b, Idro et al., 2010a). The risk of behavioral problems and epilepsy much later after an episode of severe malaria emphasizes the need for long-term follow-up in these children. Interventions like cognitive training and caregiver training to improve cognitive and behavioral problems in these children are equally important (Bangirana et al., 2009a, Boivin et al., 2013).

These neurocognitive deficits observed in children 12 months after the severe malaria episode may have an effect on the child's schooling and everyday behavior. Poor language skills are associated with difficulties in emotional regulation and problem behaviors (Vallotton and Ayoub, 2011, Qi and Kaiser, 2004), which may impair social functioning and schooling ability later in the child's life. Studies in African children show that behavioral problems appear much later after CM (Idro et al., 2010a, Birbeck et al., 2010b). It is not known how poor language skills, which appear much earlier, are associated with these

behavioral problems that appear much later. Deficits in fine motor skills may affect the child's ability to perform school activities requiring this skill such as writing, drawing, and manipulating toys. Visual reception covers abilities like visual discrimination and visual memory which if impaired may affect the child's ability to read, draw, and perform simple arithmetic tasks that require visual spatial skills and working memory (de Hevia et al., 2008, McLean and Hitch, 1999, Bangirana et al., 2013).

A limitation of all studies of CM or SMA and long-term cognition is that it is impossible to collect pre-disease neurocognitive scores on the children studied, because it is impossible to predict which children will get CM or SMA, and an enormous cohort would be required for an adequate sample of children with CM and SMA. The present study compared children with CM or SMA to age-matched community children recruited from the nuclear family, extended family, or neighborhood of the children with CM or SMA to maximize the similarity of socioeconomic and educational background, which might affect cognition (Bangirana et al., 2009b). Also, we adjusted for confounding factors that differed between the groups, which improves the likelihood that the estimated association between CM and SMA and neurocognitive impairment reflects the true association. A second study limitation is that we did not check hemoglobin level at discharge or on follow-up, so we could not determine if post-transfusion hemoglobin was related to cognition or motor function. In future studies, we plan to assess whether long-term hemoglobin levels relate to neurocognitive function. Finally, no assessment for retinopathy was done for the SMA group despite studies suggesting that over 50% of the children with SMA have retinopathy indicative of cerebral ischemia (Beare et al., 2004, Essuman et al., 2010).

5. Conclusion

CM and SMA both globally affect neurocognitive function, with significant effects in children with CM for all domains, and significant effects in children with SMA for visual reception and expressive and receptive language. Fine motor skills are more profoundly affected by CM than SMA. Further study is needed to identify the mechanisms involved in the development of long-term neurocognitive outcomes after CM and SMA, to aid development of appropriate interventions.

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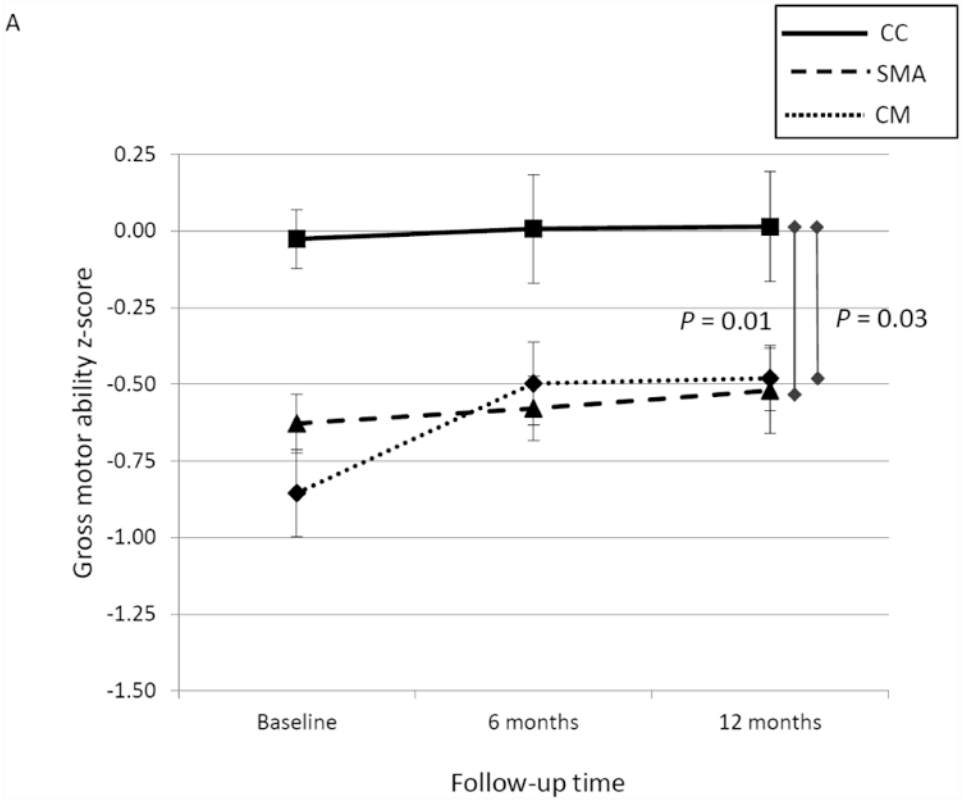
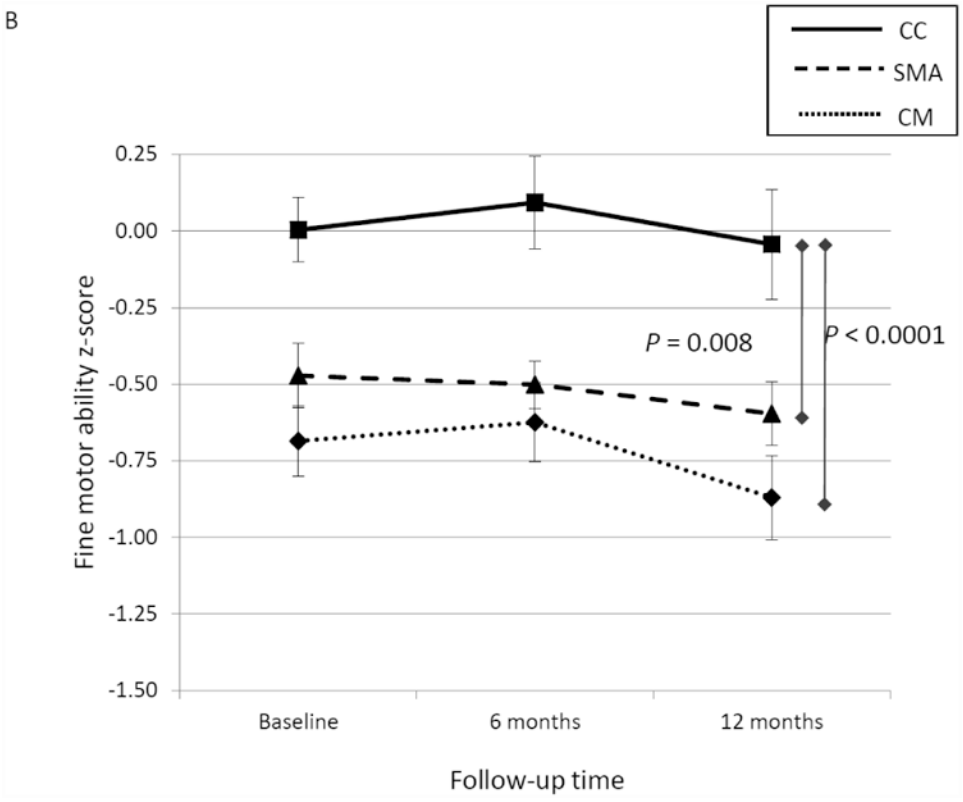
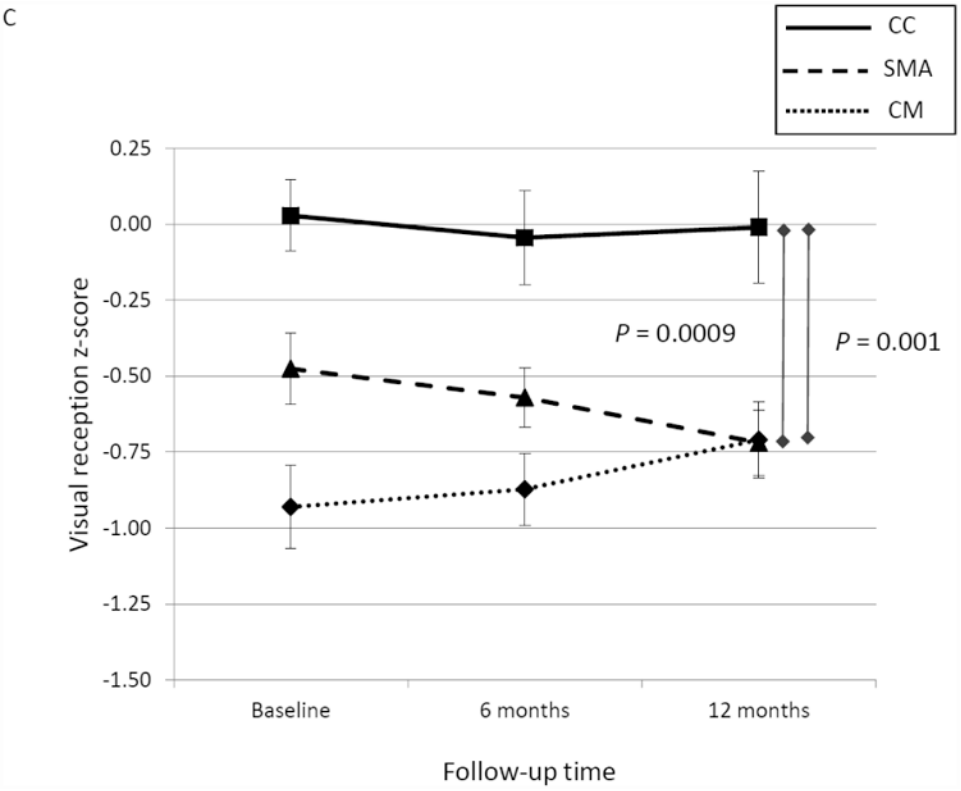
Highlights

- Children with cerebral malaria have poor neurocognition in all domains
- Children with severe malaria anemia have poor neurocognition in some domains
- Cerebral malaria affects motor skills more than severe malaria anemia
- Mechanisms of brain injury are different in both conditions

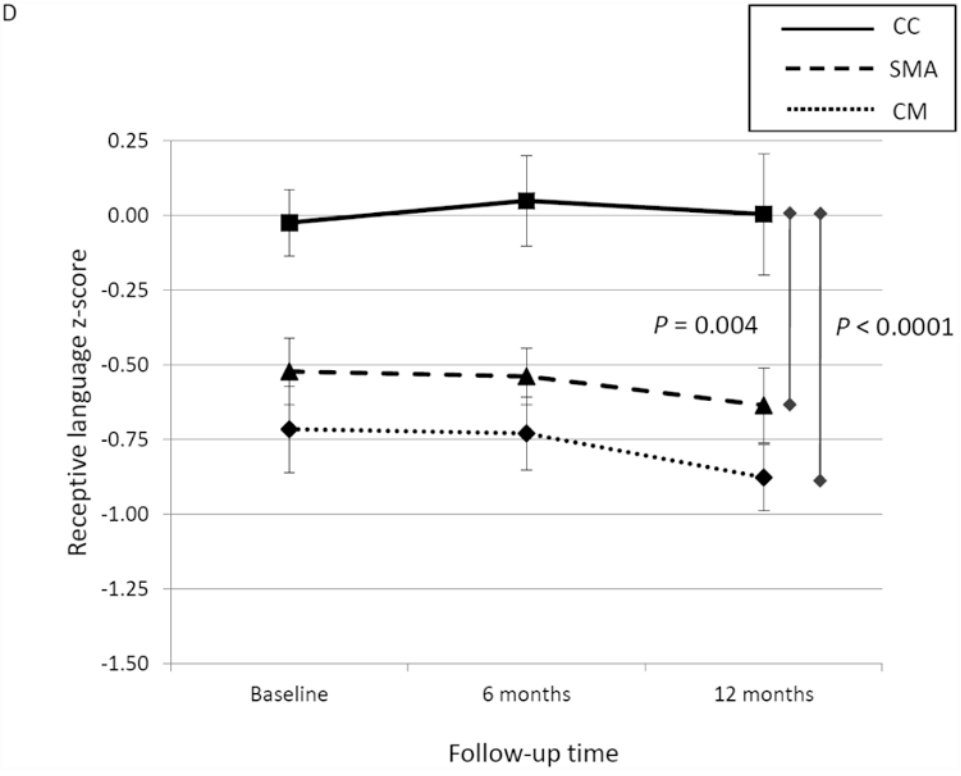




C



D



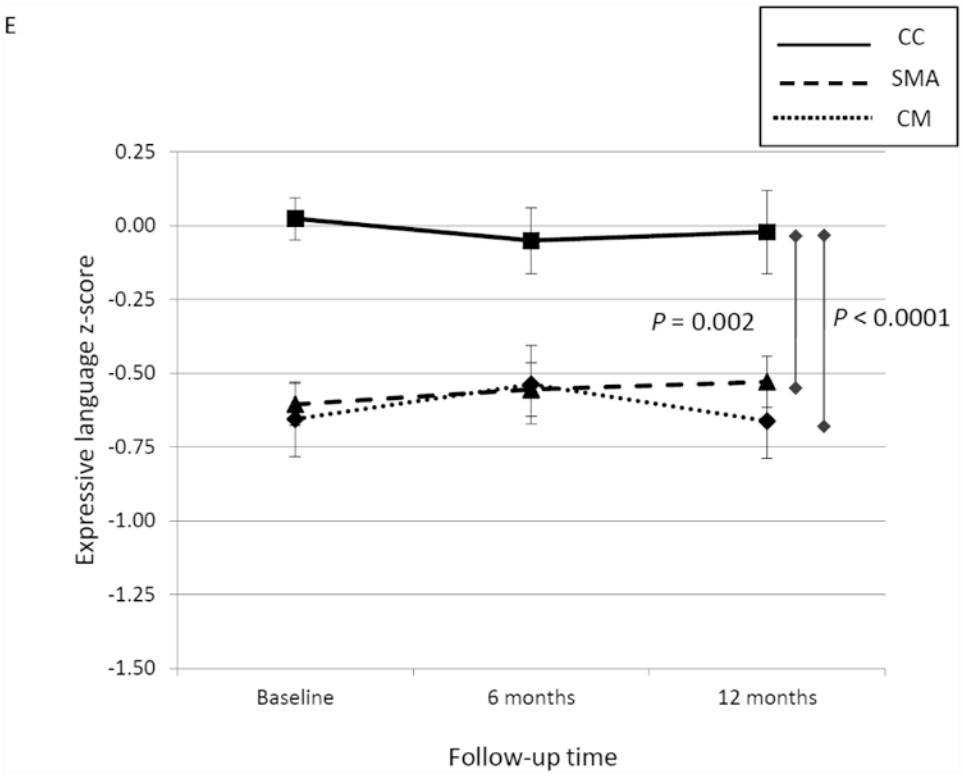


Figure 1.

Age-adjusted neurocognitive test scores in children with cerebral malaria (CM), severe malarial anemia (SMA) and community children (CC) at baseline, 6 and 12 months for gross motor ability (A), fine motor ability (B) visual reception(C), receptive language (D) and expressive language (E). Symbols depict average and standard error of average

Table 1

Demographic and clinical characteristics of study children

Characteristic		CM	SMA	CC	*p*[a]	Differences
Age (years (S.D)		2.8	25 (0.6)	2.9	<.0001	SMA<CM,
Sex (n, % female)		29	36	27	0.60	
Weight for age z-score		-1. 2	-1. 7	-0. 7	<.0001	SMA<CC
Height for age z-score		-0.5	-1.2	-1.0	0.011	SMA<CM
Socioeconomic status		8.4	9.3 (13.4)	9.5	0.06	
Hcomree environment z-		-0.1	-0.1	0.0	0.73	
Meternal education (n, %)	Primary 6 or	37	31	24	0.86	
	Primary 7	16	17	12		
	Secondary or	25	34	22		
	Not known	2 (3%)	4	3 (5%)		
Paternal education (n, %)	Primary 6 or	15	25	9	0.37	
	Primary 7	15	7 (8%)	12		
	Secondary or	33	37	26		
	Not known	17	17	14		
Child's education, pre-		6 (8%)	2 (2%)	14	0.0001	CC>CM,
Hemoglobin SS (n/total		1/77	4/83	0/61	0.23	
HIV (n/total tested %)		2/79	1/86	0/61	0.63	
Stool helminth (n,%)[b]		6/65	3/60	3/21	0.36	

Figures are mean and standard deviation unless indicated

[a]One-way ANOVA for continuous variables, Pearson's chi-square for categorical variables other than hemoglobin SS, HIV and stool helminth infection, which were compared by Fisher's exact test.

Table 2

Z-scores[a] for neurocognitive outcomes in children with cerebral malaria (CM), severe malarial anemia (SMA) and community children (CC) at 12-month follow-up and for all study visits, adjusted for age, nutrition and child education[b]

				CM - CC		SMA - CC		CM-SMA	
	CM	**SMA**	**CC**	**Mean difference (SE)[c]**	***P***	**Mean difference (SE)[c]**	***P***	**Mean difference (SE)[c]**	***P***
	Mean z-score (SE) at 12 months								
Gross motor	-0.54 (0.15)	-0.43 (0.14)	-0.07 (0.17)	-0.47 (0.23)	0.04	-0.36 (0.23)	0.12	-0.11 (0.20)	0.59
Fine motor	-0.93 (0.13)	-0.48 (0.13)	-0.12 (0.16)	-0.81 (0.21)	0.0001	-0.36 (0.21)	0.09	-0.45 (0.19)	0.02
Visual reception	-0.74 (0.14)	-0.61 (0.13)	-0.11 (0.16)	-0.63 (0.22)	0.004	-0.50 (0.22)	0.02	-0.13 (0.19)	0.50
Receptive language	-0.91 (0.15)	-0.56 (0.14)	-0.06 (0.17)	-0.86 (0.23)	0.0002	-0.50 (0.23)	0.03	-0.36 (0.21)	0.08
Expressive languagg	-0.72 (0.11)	-0.44 (0.10)	-0.09 (0.13)	-0.63 (0.17)	0.0002	-0.35 (0.17)	0.04	-0.29 (0.15)	0.06
	Mean z-score (SE) for all visits[b]								
Gross motor	-0.67 (0.12)	-0.48 (0.12)	-0.08 (0.15)	-0.59 (0.20)	0.003	-0.39 (0.20)	0.05	-0.19 (0.17)	0.27
Fine motor	-0.81 (0.12)	-0.41 (0.12)	-0.06 (0.14)	-0.75 (0.19)	<0.0001	-0.35 (0.19)	0.07	-0.40 (0.17)	0.02
Visual reception	-0.89 (0.11)	-0.49 (0.11)	-0.11 (0.14)	-0.78 (0.18)	<0.0001	-0.38 (0.12)	0.04	-0.40 (0.16	0.0121
Receptive language	-0.82 (0.13)	-0.49 (0.13)	-0.05 (0.15)	-0.77 (0.21)	0.0002	-0.44 (0.20)	0.03	-0.33 (0.18)	0.07
Expressive language	-0.67 (0.09)	-0.48 (0.09)	-0.08 (0.11)	-0.58 (0.14)	<0.0001	-0.39 (0.14)	0.006	-0.19 (0.13)	0.13

[a]Age-adjusted neurocognitive z-scores were calculated using community control children as comparator group. Nutrition was adjusted for using for weight for age z-score and height for age z-score.

[b]Mixed linear model estimates of average z-scores over enrollment, 6 months and 12 month visits. The mixed linear model analysis is a generalization of repeated measures analysis.

[c]Estimated mean difference and standard error (SE) of the estimated difference.

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Table 3

Clinical factors associated with neurocognitive ability outcomes at 12 month follow-up in children with cerebral malaria[a].

		Gross motor skills				Fine motor skills		
Clinical Factor	**Group**	**Mean (SE)**	**Pearson correlation (r)**	***p*[a]**	**Group**	**Mean (SE)**	**Pearson correlation (r)**	***p*[a]**
Categorical								
Blantyre coma score[b]	1 (n=17)	-1.55 (0.69)		0.002				
	2 (n=62)	-0.18 (0.12)						
Neuro. deficit, 6 mo	Yes (n=4)	-4.93 (2.17)		<0.0001	Yes (n=4)	-5.82 (2.11)		<0.0001
	No (n=76)	-0.25 (0.11)			No (n=76)	-0.61 (0.09)		
Neuro. deficit, 12 mo	Yes (n=3)	-5.45 (2.97)		<0.0001	Yes (n=3)	-6.27 (2.94)		<0.0001
	No (n=77)	-0.29 (0.11)			No (n=77)	-0.66 (0.10)		
Continuous								
Coma duration after admission (hours)			-0.50	<0.0001			-0.56	<0.0001
Number of seizures during admission			-0.48	<0.0001			-0.65	<0.0001
		Visual reception				Receptive language		
Clinical Factor	Group	Mean (SE)	Pearson correlation (r)	***p*[a]**	Group	Mean (SE)	Pearson correlation (r)	***p*[a]**
Categorical								
Blantyre coma score[b]	1 (n=17)	-1.71 (0.68)		0.003				
	2 (n=62)	-0.40 (0.13)						
Neuro. deficit, 6 mo	Yes (n=4)	-5.15 (1.94)		<0.0001	Yes (n=4)	-5.94 (2.01)		<0.0001
	No (n=76)	-0.48 (0.12)			No (n=76)	-0.61 (0.13)		
Neuro. deficit, 12 mo	Yes (n=3)	-5.79 (2.59)		<0.0001	Yes (n=3)	-6.88 (2.52)		<0.0001
	No (n=76)	-0.51 (0.13)			No (n=77)	-0.64 (0.14)		
Continuous								
Coma duration after admission (hours)			-0.56	<0.0001			-0.52	<0.0001
Number of seizures during admission			-0.58	<0.0001			-0.59	<0.0001

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		Gross motor skills				Fine motor skills		
Clinical Factor	**Group**	**Mean (SE)**	**Pearson correlation (r)**	***p*[a]**	**Group**	**Mean (SE)**	**Pearson correlation (r)**	***p*[a]**
			Expressive language					
Clinical Factor	Group	Mean (SE)	Pearson correlation (r)	*p*[a]				
Categorical								
Neuro. deficit, 6 mo	Yes (n=4)	-4.04 (0.98)		<0.0001				
	No (n=75)	-0.48 (0.11)						
Neuro. deficit, 12 mo	Yes (n=3)	-4.24 (1.36)		<0.0001				
	No (n=76)	-0.52 (0.11)						
Continuous								
Coma duration after admission (hours)			-0.43	<0.0001				
Number of seizures during admission			-0.56	<0.0001				

[a] Groups were compared using t tests or Pearson correlation.

[b] In 2 children the BCS score was recorded as ≤2, but the exact score was not recorded. The BCS score was 1 or 2 in all children with a recorded score (none had a score of 0).