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

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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.



## 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, Marsh, John, & Newton, 2010). Malaria with neurological involvement mainly affects attention, speech and language, memory, executive functions, and visual spatial skills (Carter et al., 2005; John et al., 2008; Kihara, Carter, & Newton, 2006). These deficits have been identified in short term and in long term as late as nine years after the illness (Boivin et al., 2007; Carter et al., 2005). Clinical and laboratory features of severe malaria associated with these deficits include coma, seizures, elevated tumor necrosis factor alpha (TNF), and hypoglycemia (Bangirana et al., 2014; Boivin et al., 2007; Idro, Carter, Fegan, Neville, & Newton, 2006; John et al., 2008). 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, Jenkins, & Newton, 2005; Idro, Marsh, John, & Newton, 2010). 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 Scales of Early Learning (Mullen, 1995), the sum of scores from fine motor, visual reception, and language domains. This single score allows for the assessment of overall neurocognitive ability but does not provide information about the individual neurocognitive domains. Also, the Mullen Scales of Early Learning 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 age, nutritional status and child's education, 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

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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) presenting with coma (Blantyre Coma Score [BCS] ≤2); 2) *Plasmodium falciparum* on the 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 the presence of *P. falciparum* on the blood smear in children with no coma or impaired consciousness and a hemoglobin level of ≤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 a hemoglobin of <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., 2009). 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 h 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 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 & 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, John, et al., 2009).

### 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 Scale 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 Scale 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 $\chi^2$ 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, Bangirana, et al., 2008). 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 to 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