**Early and middle childhood developmental, cognitive, and psychiatric outcomes of Malawian children affected by retinopathy positive cerebral malaria**

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**Abbreviations:** CBCL – Achenbach Child Behavior Checklist; CM – Cerebral Malaria; CM-R Cerebral Malaria with Retinopathy; CNS - Central Nervous System; HAZ - Height-for-Age adjusted Z score IRB – Institutional Review Board; KABC-II - Kaufman Assessment Battery for Children, 2nd edition; MDAT – Malawi Developmental Assessment Tools; SES - Socio-Economic Status; TOVA – Tests of Variables of Attention; WAZ - Weight-for-Age Z score

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**ABSTRACT**

**Objective**: To determine the short and long-term developmental, cognitive, and psychiatric effects of retinopathy positive cerebral malaria (CM-R) among young children in a prospective study assessing them around the onset of disease and again two years later.

**Methods:** One hundred and nine children were recruited from the Queen Elizabeth Central Hospital in Blantyre, Malawi, 49 with CM-R, and 60 non-malaria controls. Children were assessed for overall motor, language and social skills using the Malawi Developmental Assessment Tool (MDAT) at pre-school age. At school age, the same children were then given the Kaufman Assessment Battery for Children, Second Edition (KABC-II), which assessed global cognitive performance, and memory, as well as the Test of Variables of Attention (TOVA), which assessed attention. The Achenbach Child Development Checklist (CBCL) was administered at both time points to assess behavioral patterns.

**Results**: Controls scored significantly better on all KABC-II global domains as well as on the mental processing index than their CM-R group counterparts but showed no performance differences in the TOVA and CBCL assessments at school age, and in the MDAT and CBCL assessments at pre-school age. The MDAT total score was significantly correlated with the KABC sequential processing, learning, and mental processing index among CM-R survivors but not among controls.

**Conclusions:** Later or persisting neurocognitive effects of cerebral malaria can be captured with the KABC at school age. The MDAT at pre-school age is correlated with the KABC among CM-R survivors and can be used to capture early developmental deficits due to CM-R.

**INTRODUCTION**

Between 2010 and 2015, malaria incidence among populations at risk (the rate of new cases) fell by 21% globally. During this time, global malaria mortality rates among at-risk populations fell by 29% for all age groups, and by 35% among children under five years of age. Despite this progress, the African region still carries a disproportionally high share of the global malaria burden with 90% of malaria cases and 92% of malaria deaths. *Plasmodium falciparum* is the most prevalent malaria parasite on the African continent and is responsible for most malaria-related deaths globally (WHO 2017). Cerebral malaria (CM) is the most serious neurological complication of *P. falciparum* and occurs in over 575,000 cases of malaria and is most commonly seen in children ages 6-10 (Idro, Kakooza-Mwesige et al. 2010). While the majority of malarial cases are uncomplicated and result in a flu-like syndrome (Bartoloni and Zammarchi 2012), those inflicted with the CM can present with a rapid onset of fever, seizures, coma and brainstem signs (Idro, Jenkins et al. 2005). Importantly, retinopathy, due to the sequestration of parasitized red blood cells in the microvasculature, has been found to be the only clinical sign distinguishing malarial coma from non-malarial coma (Taylor, Fu et al. 2004). Due to the common misdiagnosis of cerebral malaria, those diagnosed and recruited into the current study were required to fit the following clinically defined criteria: presence of *P. falciparum* on blood smear, a comatose state with no other cause of coma determined, and retinopathy positive cerebral malaria (CM-R).

While most children who survive CM appear rapidly recover, about 15% are left with neurological disabilities, most commonly spasticity, ataxia, hemiplegia, speech disorders, and blindness (Birbeck 2004, Birbeck, Molyneux et al. 2010), as well as cognitive impairment, behavioral difficulties and epilepsy (Boivin, Bangirana et al. 2007, John, Bangirana et al. 2008, Boivin, Gladstone et al. 2011). In particular, children with cerebral malaria have been shown to have specific problems with attention and impulsivity well-demonstrated on a computerized test of attention (TOVA) (Boivin, Bangirana et al. 2007, John, Bangirana et al. 2008).

In a systematic review of the persisting neurocognitive effects of cerebral malaria in sub-Saharan African children, Holding and Boivin (2013) concluded that there was strong evidence from multiple studies for persisting deficits in global intellectual function, memory, conceptual reasoning, visual perceptual functions, executive functions, tactile discrimination and learning, behavior/psychological/intrapersonal functions, and academic achievement (Holding and Boivin 2013). They estimated that around 14-20% of CM survivors display impaired performance in at least one functional area two years or more after acute illness. The functional areas most vulnerable to significant impairment appear to be more complex tasks of learning and memory that depend on sustained attention. These are foundational to language development, and may well explain the effects of CM on language development (Boivin, Gladstone et al. 2010).

Bergemann et al. (2012) noted that the assessment of the effects of disease on neurocognitive outcomes in children over time presents several challenges because standardization and validation is required for tests developed originally in high-income countries (Bergemann, Bangirana et al. 2012). They used assessment measures completed with school-age Ugandan cerebral malaria survivors longitudinally (Boivin, Bangirana et al. 2007, John, Bangirana et al. 2008). At that time, these findings were based on the only prospective study of the persisting neurocognitive effects of cerebral malaria in children assessed longitudinally. In her re-analyses of these findings, Bergemann applied statistical techniques to age-standardize these outcomes over time for an index of working memory, executive attention and tactile learning. These were transposed for three cohorts (cerebral malaria, uncomplicated malaria, community controls) at hospital discharge/enrollment, and at 3-, 6- and 24-month follow-up. Using this statistical approach to normalize for age, the cerebral malaria survivors remained significantly below the uncomplicated malaria and community control comparison groups in a more consistent manner. This led Bergemann and colleagues to conclude that the neurocognitive deficit trajectory through two years of longitudinal follow-up for cerebral malaria was stable and did not improve.

Although such persisting neurocognitive deficits in cerebral malaria survivors were identified years after the acute illness event, such deficits were related to various clinical indicators of severity of acute illness in the surviving children. These clinical factors included length of coma and amount of seizure during illness (Idro, Carter et al. 2006, Abubakar, Van De Vijver et al. 2007, John, Bangirana et al. 2008), severity of malaria-specific retinopathy during illness (Boivin, Vokhiwa et al. 2014), intensity of pro-inflammatory immunopathogenic biomarkers such as TNFalpha during illness (John, Panoskaltsis-Mortari et al. 2008), and even the buffering effect of post-illness cognitive rehabilitation in the form of the amount of schooling after illness (Holding, Taylor et al. 2004), or computerized cognitive rehabilitation training (Bangirana, Boivin et al. 2013).

However, no studies have looked at both the neurodevelopment at pre-school age and cognition at school age of children affected by cerebral malaria, using different assessment tools over time. Our previous work has evaluated the neurodevelopmental effects of cerebral malaria in preschool-age children in both Malawi (Boivin, Gladstone et al. 2010) and Uganda (Bangirana, Opoka et al. 2014, Bangirana, Opoka et al. 2016). We have also evaluated the longitudinal effects of cerebral malaria in surviving school-age children in Malawi (Boivin, Vokhiwa et al. 2014) and Uganda (Boivin, Bangirana et al. 2007, John, Bangirana et al. 2008, Bangirana, Allebeck et al. 2011, Bergemann, Bangirana et al. 2012). The present study goes beyond these previous reports, however, in that we evaluate the correspondence between our neurodevelopment preschool-age findings between CM-R and control cohorts, and the neuropsychological school-age findings for these same children. We do so for both the cognitive *and* psychiatric outcomes at preschool and school-age, which is also unique to our present study.

There is consensus that valid and relevant early developmental measures are predictive of neuropsychological and cognitive performance in middle childhood and beyond (Pollitt 1999, Sutcliffe, Soo et al. 2010). However, these is less evidence for such predictive validity of early developmental assessments for school-age cognitive and behavioral outcomes, with children in resource-constrained settings for African children at risk from infectious disease, poor nutrition, or other factors such as toxic environmental exposures (Boivin, Kakooza et al. 2015, Suchdev, Boivin et al. 2017). Although newly adapted developmental assessment tools have been designed to be culturally more appropriate (Sabanathan, Wills et al. 2015), their correspondence validity to school-age measures remains mostly unknown (Kammerer, Isquith et al. 2013, Semrud-Clikeman, Romero et al. 2017). This study is the first to address that issue with sub-Saharan African children who have survived cerebral malaria (CM).

 First, we report on developmental, cognitive, and psychiatric outcomes of Malawian children who survived CM at a young (first 5 years of life) age, a time during which the brain is rapidly developing (Boivin, Gladstone et al. 2011). Severity of acute cerebral malaria illness in the preschool years as measured by the degree of malaria-specific retinopathy (CM-R) was predictive of later cognitive disability in this cohort of children (Boivin, Vokhiwa et al. 2014). The present study compares preschool development and school-age cognitive and behavioral performance in a subgroup of these same cohorts of CM-R survivors and control children. Furthermore, the present study will also evaluate the correspondence or predictive validity between the preschool child development and school-age cognitive performance measures previously published for these cohorts, for the CM-R and control children separately.

**METHODS**

**Study participants and recruitment.** The study was performed at the Blantyre Malaria Project at the Queen Elizabeth Central Hospital in Blantyre, Malawi, which is the national referral teaching hospital. Control group participants and those with CM-R for this study were a subgroup of children from a larger study (Boivin, Gladstone et al. 2011) who eventually went on to complete a school-age neuropsychological and behavioral assessment following their preschool-age assessment. Children from this larger study were recruited from an exposure-control study designed to compare rates of epilepsy development in children who survived CM-R (Birbeck, Beare et al. 2010, Birbeck, Molyneux et al. 2010). CM-R is defined as: 1) coma (Blantyre Coma Score [BCS] ≤ 2;), 2) *Plasmodium falciparum* on blood smear; 3) no other known cause of coma (e.g., hypoglycemia-associated coma reversed by glucose infusion, meningitis, or a prolonged post-ictal state); and 4) retinopathy positive, as determined a trained ophthalmologist, defined by the presence of hemorrhages, papilledema, disk hyperemia, central retinal whitening in the macula and foveal annulus, peripheral whitening by eye quadrant, and vascular abnormalities in the arteries/veins or capillaries in both eyes were noted and each participant was rated on overall severity from 0 to 3+ (Boivin, Vokhiwa et al. 2014).

Forty-nine CM-R confirmed participants completed both a developmental test at pre-school age and a neuropsychological test at school age as a part of these studies (Boivin, Gladstone et al. 2011, Boivin, Vokhiwa et al. 2014). Sixty-two children in the control group were also assessed at two time points with a developmental and a neuropsychological test at the Blantyre Malaria Project Center, Queen Elizabeth Central Hospital. Two children who developed CM-R between pre-school and school-age assessments were excluded from this analysis, leaving 60 controls with the same CM-R-negative status at both time points. Additional exclusion criteria for all children included: 1) known chronic illness requiring medical care; 2) known developmental delay; 3) prior history of coma, head trauma, hospitalization for malnutrition or cerebral palsy; and 4) HIV infection. Additional exclusion criteria for control group included: 1) illness requiring medical care within the previous four weeks and 2) major medical or neurological abnormalities on screening physical exam. Informed written consent was obtained from the parent or principal caregiver of each participant by Malawian research nurses in the local language of Chichewa. Children seven years of age and older provided written assent. Institutional Review Board approval for this study was granted by Michigan State University and the College of Medicine for the University of Malawi.

**Assessments.** A standard physical examination and medical history was completed for each child. Height and weight were measured and standardized into weight- or height-for-age z-scores (WAZ or HAZ) using the Epi Info WHO 2010 database for physical development. Socioeconomic status (SES) was determined using a series of questions answered by the caregiver about parental educational and occupational status, as well as the quality of the home environment, material possessions, and food security.

**Assessment for pre-school children**

**Malawi Development Assessment Tool (MDAT).** Participants’ cognitive development was measured using the culturally appropriate Malawi Development Assessment Tool (MDAT) developed by Gladstone et al (2010). The MDAT uses four domains: gross motor, fine motor, language and social skills. 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, Lancaster et al. 2010). After ensuring the child was not ill, the MDAT was administered by two trained research nurses in a private evaluation room. The examiners used the floor and ceiling methodology whereby for each domain, the child must pass seven items in a row below the child’s development age to continue. Scoring was discontinued when the child received no credit for seven consecutive items. A raw score for each domain of development was converted into a Z-score in relation to a normative Malawian sample (Boivin, Gladstone et al. 2011), and the average of the z-scores for each domain was used to compute the MDAT total score.

**Achenbach Child Development Checklist (CBCL) Pre-school.** The CBCL is a widely used caregiver instrument measuring behavioral problem in children by both internalizing symptoms (e.g. depression, anxiety, withdrawal, somatic complaints) and externalizing symptoms (e.g. aggressiveness, obstinacy and psychosocial deviance). The Achenbach CBCL has also been shown to be reliable for use in clinical pediatric populations in sub-Saharan Africa (Familiar, Ruisenor-Escudero et al. 2015). The preschool version of the CBCL, used for children aged 1.5–5 years (Achenbach and Rescorla 2000), was translated into the local language of Chichewa independently by three individuals trained in psychology (one at the Bachelor’s degree level, one at the Master’s degree level, and one at the PhD level). Any discrepancies in the three translations were resolved by a consensus panel of two Malawian research nurses and co-author MV. The research nurse read the CBCL items aloud to the principal caregiver privately in a separate room during the child’s developmental assessment, or else afterwards if the mother needed to be present with the child. The total number and type of symptoms from the internalizing and externalizing domains along with total symptoms, were recorded for each participant and were standardized using the cross-cultural norms that are available for this measure (Achenbach 2010).

**Assessment for children attending school**

**Kaufman Assessment Battery for Children (KABC-II).** The Kaufman Assessment Battery for Children, second edition (KABC-II) was used for the assessment of memory and cognitive deficits. The KABC-II has four global performance domains and assesses higher order tasks: sequential processing (working memory), simultaneous processing (visual processing), planning ability (fluid reasoning) and learning ability (long term memory and retrieval) (Kaufman and Kaufman 2004). In the Luria neuropsychological model for scoring and interpreting the KABC-II, these four global domains are combined to form a global composite performance measures called the Mental Processing Index (MPI), which evaluate the child’s overall cognitive ability. The KABC-II has been well validated in the Sub-Saharan African context

**Tests of Variables of Attention (TOVA).** The TOVA visual test is a computerized, objective test of attention consisting of a smaller black square presented rapidly and randomly within a larger white square, either at the top (signal) or at the bottom of the larger square (non-signal). The child presses a switch as quickly as they can with their dominant hand in response to the signal, and should withhold responding to the non-signal. In addition to providing an ADHD score, variables measured in the TOVA include: variability of response time, response time, commission, errors of omission, representing consistency, impulsivity and inattention, respectively, as well as post-commission response times, multiple and anticipatory responses (Greenberg 1993). This measure was chosen due its previously shown sensitivity to the effects of cerebral malaria in Senegalese and Ugandan children (Boivin, Bangirana et al. 2007, John, Bangirana et al. 2008, Bergemann, Bangirana et al. 2012).

**Achenbach Child Behavior Checklist for Children Attending School (Parent Questionnaire).** The school-age CBCL has been validated with cerebral malaria survivors in Uganda (Bangirana, Nakasujja et al. 2009).As with the pre-school CBCL, the school version of the CBCL, appropriate for school-age children, was translated into the local language and any discrepancies in translation were reconciled by a consensus panel. However, it should be noted that in evaluating the discrepancies in back translation, concerns were raised as to whether some of the items were culturally appropriate or could be readily understood by Malawian mothers in evaluating their children. The school-aged CBCL was administered to the principal caregiver in a separate room during the child’s neurocognitive assessment, and the cross-cultural norms were used to standardize the Internalizing, Externalizing, and Total Symptoms outcomes (Achenbach and Rescorla 2007).

**Data Analysis.** T- and chi-square tests were used to compare CM-R and control children on sociodemographic and anthropometric characteristics at intake (Table 1). Analysis of covariance (ANCOVA) was used to compare the control and the CM-R groups on developmental, cognitive, and psychiatric outcomes evaluated at pre-school and school-age assessments (Table 2). All models included adjustment for SES. Sex was also used as a covariate in the analyses of age-standardized scores MDAT and KABC scores. This was decided on a priori because of previous associations noted between SES and sex with some of the KABC outcomes in Ugandan CM survivors (Bangirana, John et al. 2009). In the analyses of sex-standardized TOVA ADHD index, the covariates included age at the time of testing, and both age and sex were included as covariates for other TOVA scores. We have also explored adding weight-for-age z scores (WAZ) or height-for-age z scores (HAZ) (World Health Organization - WHO 2010 norms) as covariates because of the potential association between physical growth and neurodevelopment in at-risk sub-Saharan African children, including CM survivors (Abubakar, Van De Vijver et al. 2007, Abubakar, Van de Vijver et al. 2008, Abubakar, Holding et al. 2009). The least square (LS) means for the CM-R and controls groups were compared. To facilitate the interpretation of the group differences, the adjusted effects sizes (Cohen’s d) were computed as differences between the LS means divided by the adjusted standard deviation (square root of the mean squared error).

The strength of relationship of preschool global development test (MDAT) to our school- age cognitive tests (KABC, TOVA) was quantified using Pearson correlation coefficients within the CM-R and control groups. Similarly, we correlated pre-school and school-age CBCL scores. Given the available sample size, power was sufficient (0.80 or greater in two-tailed tests at 0.05 level of significance) to detect group differences of 0.54 of the standard deviation or larger. The magnitude of correlations between pre-school and school-age measures detectable as statistically significant was 0.34 for the control children and 0.38 for the CM-R children.

**RESULTS**

Of the 109 children who completed both the preschool and school-age assessments, 60 (55%) were boys. The average age for children at preschool assessment was just over 4 years (range 1.92-6.83), and about 6.5 years of age at the follow-up assessment (range 3.67-8.00) (Table 1). The average time span from pre-school to school- age assessment was approximately two years (Table 1) and ranged from 1 to 60 months for the control and 1 to 49 months for the CM-R children. For the CM-R children, the average interval in months between acute CM illness and preschool assessment was 17.9 (range 1 to 41 months) and 46.6 (range 24 to 71) for the school-age assessment. These assessment intervals varied because children in the present study were enrolled following protocol completion in a separate clinical study of epilepsy for CM survivors and matched controls (Birbeck, Molyneux et al. 2010). There were no differences in demographic characteristics between CM-R and control groups (Table 1).

Although both the control and CM groups of children were below the Malawian normative mean (z = 0; SD=1) on the MDAT as witnessed by their negative average z scores, they were well within 1 SD (normal range) on average z-score performance for all four developmental domains (Table 2). At the time of pre-school assessment, no statistically significant differences were found between CM-R and control groups. The adjusted effect sizes for group differences were approximately ¼ of the adjusted standard deviation for all MDAT scores except social skills.

At school age, groups significantly differed on all KABC-II global domains as well as on the mental processing index, with the effect sizes of ½ of the adjusted standard deviation or greater. The normative standard deviation for the global domains for the KABC-II is SD=15, and the CM-R children were about 2 SDs below the mean of 100 on average for the KABC-II MPI score (Table 2). This indicates a clinically meaningful deficit for this group. In the present analyses, the two groups did not differ on TOVA or CBCL, and the effect sizes for group differences were small (Table 2). For the CBCL, both groups were well within a normal range (mean =50) for reported psychiatric symptoms. However for the TOVA, both groups had very low TOVA ADHD index scores (the further below a score of zero – which is based on American children - the worse the performance). Both groups of children in the present study also were well below average on the signal detection D prime measure of attention performance for this test, as compared to control children from other African-based studies using the TOVA assessment (Boivin, Barlow-Mosha et al. 2018). These results did not change in an appreciable manner with the adjustment for WAZ or HAZ, therefore the LS means reported in Table 2 are adjusted for sex and SES, as well as age for outcomes not standardized for age.

The MDAT total score correlated significantly with the KABC sequential processing and learning scores, as well as the mental processing index among CM-R survivors. The correlations between the MDAT and KABC scores were weak and not statistically significant among control children. This was also the case with the correlations between the MDAT and TOVA for both CM-R and control groups. The correlations between pre-school and school-age CBCL were moderate and statistically significant, except for the internalizing problems score in the CM-R group (Table 3).

**DISCUSSION**

 The present study is the first to evaluate both preschool-age neurodevelopmental and school-age neuropsychological deficits in a prospective study of a single cohort of retinopathy-confirmed CM survivors. Previous research has shown that those who survive cerebral malaria can have long-term cognitive impairment, both at the onset of disease and upon long term follow-up through middle childhood (Holding and Boivin 2013). In contrast to our findings with these cohorts in our previous analyses (Boivin, Gladstone et al. 2011), differences between CM-R survivors and controls were not statistically significant at pre-school age with the MDAT. The present study only included children who were also evaluated at school-age with the KABC and TOVA tests, and additional exclusion criteria were applied in the present analysis. As a result, the sample size for preschool-age comparison was smaller in the present study, and differences of 0.54 of the standard deviation or greater were detectable as statistically significant. Observed differences between CM-R and control children on the MDAT in this sample were at or near 0.25 of the standard deviation.

In the Boivin et al (2011) comparison between the CM-R and control cohorts, percent of children developmentally delayed for each of the MDAT scales was analyzed. This determination was based on the normative data available for this test with Malawian children using the original full version of the test (Gladstone, Lancaster et al. 2008, Gladstone, Lancaster et al. 2009). However, the present analysis used re-computed standardized scores based on norms for the final version of the MDAT test (Gladstone, Lancaster et al. 2010). Even though the new standard scores were different from the original scores used in the 2011 analyses, they were still very strongly correlated (r > 0.90) for all of the scales. The differences in findings from Boivin et al (2011) and present paper could be due to the exclusion of children with infections and illnesses that would likely affect brain function (e.g., HIV) in the present sample. The determination of HIV and other infections was available for the time period between pre-school and school-age assessments. This brings to light important considerations in the longitudinal assessment of children from very early through middle childhood. Children in such settings are faced with a myriad of risk factors that can give rise to illnesses and injury, threatening the integrity of brain/behavior function and diminishing the extent to which normal developmental performance in early childhood is predictive of later neurocognitive performance in the face of an intervening impairment.

In contrast to the MDAT, differences on the KABC at school age were significant with the effect sizes twice as large compared to the early differences on the MDAT. This demonstrates the persistent neurocognitive impairment due to the impact of cerebral malaria on the brain. This result is in line with other published findings with Ugandan preschool children that consistently documented neurodevelopmental deficits in CM surviving preschool-age Ugandan children (Bangirana, Opoka et al. 2014, Bangirana, Opoka et al. 2016) and extending into their school-age years in cross-sectional comparisons with different cognitive performance tests (Bangirana, Menk et al. 2013). Other studies have done so using the KABC, TOVA, and Tactual Performance Test (TPT; measure of tactile-based learning) in a repeated-measures prospective study of school-age Ugandan children (Boivin, Bangirana et al. 2007, John, Bangirana et al. 2008, Bergemann, Bangirana et al. 2012). Our present findings revealed much more significant neurocognitive differences with the KABC-II test at the school-age assessment, but not with the TOVA attention and impulsivity measures.

Holding and Boivin (2013) present a structural equation model of the KABC and TOVA principal outcome measures, as they relate to quality of home environment, malnutrition, and a history of cerebral malaria (Figure 12.3 on page 262) (Holding and Boivin 2013). The model was consistent across four countries: Senegal (Boivin 2002), Kenya (Holding, Stevenson et al. 1999), Uganda (Boivin, Bangirana et al. 2007), and Malawi (Boivin, Vokhiwa et al. 2014).

Ugandan school-age CM survivors presented with significantly poorer TOVA attention performance (Boivin, Bangirana et al. 2007, John, Bangirana et al. 2008), but these children were not examined for malaria-specific retinopathies (i.e., retinopathy positive) for confirm diagnosis for CM during acute illness. Because one out of four children may meet the criteria for cerebral malaria but in fact be in coma for other causes of brain infection (Taylor, Fu et al. 2004), funduscopic examination for malaria-specific retinopathy provides a highly sensitive and specific means of diagnosing “true” cerebral malaria (Birbeck, Beare et al. 2010). This was the case for the CM cohort included in the present study. Furthermore, severity of malaria-specific retinopathy during acute illness was significantly predictive of both KABC-II and TOVA neurocognitive deficits in our present Malawian cohort, even years after CM illness (Boivin, Vokhiwa et al. 2014).

The present findings for our Malawian CM cohort differ from those of the Ugandan studies in that among Malawian children neurodevelopmental differences between CM-R survivors and controls were weaker at preschool age, and our KABC cognitive differences at school age were greatest for memory and learning, but minimal for the TOVA attention measures. The differences on the TOVA test findings between our previous Uganda and the present Malawian study samples could be due to contextual and sampling differences in TOVA testing, especially in terms of the control groups. Also, in contrast to present study that found no group differences in CBCL at both time points, persisting behavioural and psychiatric problems have been reported with Ugandan CM survivors (Idro, Kakooza-Mwesige et al. 2016).

Studies with Kenyan pre-schoolers have also documented significant relationships between weight for age measures of growth, gross motor development, and long-term neurodevelopmental trajectories in impoverished and HIV-affected populations (Abubakar, Holding et al. 2008, Abubakar, Van de Vijver et al. 2008, Abubakar, Holding et al. 2009, Abubakar, Holding et al. 2009). One study of Kenyan CM survivors also documented that preschool growth and motor development was significantly predictive of long-terms neuropsychological outcomes (Abubakar, Van De Vijver et al. 2007). In our present study, we ran the analysis of covariance models with and without weight-for-age z-scores (WAZ), and the results did not change in an appreciable manner. It should be noted that CM does not directly cause poorer WAZ, although children from poorer economic conditions who are more malnourished may also be more at-risk from complicated malaria (Idro, Ndiritu et al. 2007).

In this study we also evaluated the correspondence validity of the pre-school developmental assessment using the MDAT, with neuropsychological outcomes measured at least several years after acute illness, using the KABC and the TOVA. We found that neurodevelopmental status as measured by the MDAT was significantly correlated with school-age performance on the KABC-II Sequential Processing (working memory), Learning, and Mental Processing Index (composite of overall cognitive ability) among CM-R survivors but not among control children. These findings confirm previously well documented evidence as to the greater sensitivity of developmental assessments to neurocognitive disability later in childhood, particularly in developmentally delayed children. As back as far as the 1950’s Illingworth reported such findings in terms of the longitudinal outcomes of children who were in the extreme tails of the normal distribution for development. If they were exceptionally low or high in the developmental curve early on, their early development measures were predictive of their cognitive abilities later in childhood. This was not the case for younger children well within the “normal” range of development early on (Illingworth 1958, Illingworth and Birch 1959).

Other recent studies that have evaluated preschool to school-age development and cognitive abilities with different tests in the same cohort. Torras-Mana and colleagues (2016) evaluated the extent to which the Bayley-III scales could predict later cognitive performance in Spanish children diagnosed with Autism Spectrum Disorder (ASD). Children assessed with the Bayley-III before 42 months of age were evaluated again between 4 and 5 years with one or more of several other test batteries including the McCarthy Scales of Children’s Abilities, the Kaufman Assessment Battery for Children (1st edition) (K-ABC), or the Illinois Test of Psycholinguistic Abilities (ITPA) (Torras-Mana, Gomez-Morales et al. 2016). Lower scores on the cognitive and language Bayley-III scales before 3.5 years of age predicted lower cognitive and oral language levels at 4 years of age, with significant correlations obtained between the Cognitive Bayley-III Scale and the General Cognitive MSCA Scale and the K-ABC Mental Processing Composite. The present study extends these study findings in evaluating the predictive validity of the MDAT in African children surviving cerebral malaria. This is despite the fact that the MDAT is a far less comprehensive and in-depth an evaluation of language and cognitive development than the Bayley-III, considered by many to be the gold standard in neurodevelopmental assessments (Kammerer, Isquith et al. 2013).

Although Alan Kaufman was a key investigator in the design and validation of the Wechsler Intelligence Scale for Children (WISC), he and his wife Nadeen Kaufman designed the KABC (1st edition) so as to be more culturally fair and less confounded by academic achievement than the WISC. This has been borne out in a number of dissertation cross-cultural studies comparing the WISC and the KABC (Kaufman and Kaufman 1983). The MDAT was specifically designed and validated by Melissa Gladstone as her doctoral thesis, as a means of measuring child development in the Malawian context (Gladstone, Lancaster et al. 2008, Gladstone, Lancaster et al. 2010). For that reason, we expected the correspondence validity to be stronger for the MDAT and KABC-II than might be expected for the Bayley and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) or WISC in the Malawian context. Although this can only be considered a preliminary study, our hypothesis of correspondence validity has been supported among CM-R survivors.

An explanation for the lack of correspondence validity among controls may be that in the absence of significant developmental risk, such as the one from cerebral malaria in the preschool years, other more distal developmental factors (e.g., nutrition quality, maternal literacy and quality of caregiving, level of schooling) may moderate the sensitivity of the MDAT to school-age cognitive ability performance as measured by the KABC-II. Longitudinal imaging of the developing brain from four to 21 years has demonstrated that lower order somatosensory and visual cortical areas develop earlier than higher order functions (Gogtay, Giedd et al. 2004). Basic motor and sensory functions develop earlier, followed by areas involved in speech, spatial orientation, language and attention. The last to develop are executive functions, motor coordination and attention (Gogtay, Giedd et al. 2004). The MDAT is composed of tests for motor, fine motor/vision, language, and social development. These correspond with the skills that appear earlier (Boivin, Gladstone et al. 2011). The KABC-II evaluates neurocognitive performance (memory, visual-spatial analysis and problem solving, learning, planning). The MDAT was not predictive of the KABC-II global domain of reasoning for the CM-R children in the present study, perhaps because this is an executive function domain of the developing brain that more clearly emerges only in middle childhood in Malawian children (Laine, Tuokkola et al. 2009, Baddeley 2012, Allen, Baddeley et al. 2014).

In this study, strong associations were seen between pre-school and school-age Achenbach CBCL scores with no differences between CM-R and control groups, confirming strong predictive validity between the CBCL preschool and school-age versions. Our results suggest that careful attention needs to be given to the selection of tests so that similar or at least related constructs are measured at various time points (Semrud-Clikeman, Romero et al. 2017). Selection of these tests requires consideration of both the age of the children to be assessed and whether the construct is appropriate to measure for the insult that has occurred (Sabanathan, Wills et al. 2015). Also, few neuropsychological studies have evaluated the consistency and validity of their measures cross-culturally across different African contexts, although there are some notable recent examples of this kind of assessment work (Holding, Anum et al. 2016, Boivin, Barlow-Mosha et al. 2018). In fact, the Kaufman Assessment Battery for Children is perhaps the most validated assessment battery cross-culturally in the African context, especially in the neurocognitive evaluation of cerebral malaria and of pediatric HIV (Giordani, Boivin et al. 1996, Ochieng 2003, Bangirana, Seggane et al. 2009, Boivin and Giordani 2009, van Wyhe, van de Water et al. 2017).

This study is limited by the varied assessment intervals of both the pre-school and school-age measures after acute illness of cerebral malaria. For the school-age battery, we measured a narrow range of abilities leaving out other important areas like language and motor function, which were areas of development measures by the MDAT, and identified as important areas of potential developmental delay in the aftermath of cerebral malaria (Boivin, Gladstone et al. 2010, Holding and Boivin 2013). The non-malaria cohort evaluated in Boivin et al (2011) was originally recruited from the pediatric ward of Queen Elizabeth Central Hospital so as to be age matched to the cerebral malaria children (Birbeck, Molyneux et al. 2010). A present study limitation is that our non-malaria control group may not be representative of the more general population of Malawian children due to the additional exclusion criteria for this longitudinal follow-up.

Despite these limitations, the study findings inform measurement choices for future evaluation of interventions to support neurodevelopment and improve neurocognitive function. Severe malaria in early childhood is one of many infectious diseases of the brain contributes to significant long-term disabilities in resource-constrained tropical regions of the world (Boivin, Kakooza et al. 2015). The median age of children hospitalized with severe or complicated malaria in Malawi is about three and a half years (Birbeck, Molyneux et al. 2010). Early childhood development (ECD) programs are being promoted globally by UNICEF and WHO, and typically consist of both nutritional intervention and caregiver training for cognitive enrichment in the home (Black, Walker et al. 2017). Such programs have been implemented in rural areas of Malawi where children are impoverished and very much at risk (Gelli, Margolies et al. 2017). These have been documented to enhance child development and caregiver emotional wellbeing in HIV-affected rural Ugandan households (Boivin, Bangirana et al. 2013, Boivin, Bangirana et al. 2013, Bass, Opoka et al. 2017, Boivin, Nakasujja et al. 2017) and could provide an intervention model for children developmentally at risk from chronic malaria and anemia (Boivin, Sikorskii et al. 2016).

Computer cognitive games training have been used to enhance attention, visual-spatial processing, and working memory in Ugandan cerebral malaria survivors (Bangirana, Giordani et al. 2009, Bangirana, Boivin et al. 2013). These have also been evaluated in clinical trials, as a way to enhance neurocognitive function in children with HIV (Boivin, Busman et al. 2010, Giordani, Novak et al. 2015, Boivin, Nakasujja et al. 2017). Our present findings with Malawian school-age children surviving CM imply that effective rehabilitative interventions to enhance attention, working memory, and planning/reasoning are very much needed (Boivin and Giordani 2009, Boivin, Dobias et al. 2013).

**CONCLUSIONS**

This current study further confirms the long-term neurocognitive effects of retinopathy positive cerebral malaria, especially in the areas of memory and executive functioning. Furthermore, it has shown that culturally appropriate measures of development such as the MDAT administered near the onset of CM-R (pre-school aged) can provide measures of development that are reasonably associated with later life (school-aged) cognitive performance. However, such relationships may be more apparent in the context of early risk factors compromising brain/behavior integrity. Children that are identified as having neurodevelopmental problems post cerebral malaria in the pre-school period have a heightened risk for the impaired neurocognitive outcomes at school age, and need interventions to support and enhance the neurocognitive development. We would advocate that for these children, early identification of developmental difficulties should be considered post-discharge through regular follow up clinics, that all parents and children who are identified should be provided with support and information and should be linked to appropriate services available in their setting (Bangirana, Idro et al. 2006). Even just providing information on the condition and the long-term consequences can be helpful to parents (Paget, Mallewa et al. 2016, Kambale, Ali et al. 2017, Mbale, Taylor et al. 2017). Furthermore, many parts of the world have programmes which can at least provide community advice, special needs support, integrated schooling and in some circumstances, therapies (Aboud and Yousafzai 2015). If these were considered earlier, the trajectory for these children might be different.

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**Table 1.** Comparison of demographic and anthropometric characteristics of control and cerebral malaria retinopathy (CM-R) groups.

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic\*** | **Control, N=60** | **CM-R, N=49** | **P-value** |
| Age at preschool assessment | 4.12 (1.25) | 4.35 (1.03) | 0.31 |
| Age at school assessment | 6.15 (1.21) | 6.33 (1.03) | 0.42 |
| Months between cerebral malaria hospitalization and testing: Preschool |  | 17.88 (11.84) | N/A |
| Months between cerebral malaria hospitalization and testing: School age |  | 46.62 (11.77) | N/A |
| Months between Preschool and School Age testing | 25.45 (11.04) | 23.99 (10.75) | 0.43 |
| Male sex, N (%) | 35 (56%) | 25 (53%) | 0.73\* |
| Weight in kg at preschool assessment | 14.34 (2.51) | 15.00 (2.01) | 0.14 |
| Height in cm at preschool assessment | 95.50 (9.56) | 97.92 (7.55) | 0.09 |
| Weight-for-age z-score (WHO 2010 norms) at preschool assessment | -2.46 (1.00) | -2.41 (0.79) | 0.78 |
| Height-for-age z-score at preschool assessment | -4.02 (1.54) | -3.82 (1.30) | 0.48 |
| Socio-economic status total score  | 7.40 (2.09) | 7.12 (2.13) | 0.50 |

Group means and standard deviation reported unless noted otherwise. *P* values are for Student *t* test for except for Male sex, where *p* value for chi square test is presented.

**Table 2.** Comparisons of developmental, cognitive and psychiatric outcomes of control and cerebral malaria retinopathy (CM-R) groups at pre-school and school-age assessments. Group unadjusted and least squares (LS) means and 95% confidence intervals (Cis) are presented for the Malawi Developmental Assessment Tools (MDAT) standardized z scores, Achenbach Child Behavior Checklist (CBCL) T scores, Kaufman Assessment Battery for Children (KABC) 2nd edition standardized scores, Test of Variables of Attention (TOVA) covariate-adjusted scores.

|  |  |  |
| --- | --- | --- |
|  | **Unadjusted** | **Adjusted** |
| **Outcome** | **Control, N=56****Mean (95% CI)** | **CM-R, N=47,****Mean (95% CI)** | **Effect size for the difference ,****CM-R=referent,*****p*-value** | **Control, N=56****LS Mean (95% CI)** | **CM-R, N=47,****LS Mean (95% CI)** | **Effect size for the difference ,****CM-R=referent, *p*-value** |
| Pre-school assessment |
| MDAT gross motor z-score | -0.18(-0.46, 0.10) | -0.50(-0.93, -0.07) | 0.25,0.22 | -0.17(-0.50, 0.17) | -0.50(-0.86, -0.13) | 0.25,0.19 |
| MDAT fine motor z-score | -0.29(-0.69, 0.11) | -0.66(-1.12, -0.20) | 0.24,0.22 | -0.28(-0.69, 0.13) | -0.65(-1.10, -0.20) | 0.23,0.97 |
| MDAT language/hearing z-score | -0.02(-0.39, 0.35) | -0.34(-0.71, 0.02) | 0.24,0.22 | -0.01(-0.36, 0.35) | -0.33(0.72, 0.05) | 0.24,0.22 |
| MDAT social skills z-score | -0.43(-0.82, -0.04) | -0.49(-0.85, -0.12) | 0.04,0.83 | -0.40(-0.76, -0.04) | -0.46(-0.85, -0.06) | 0.04,0.85 |
| MDAT overall total z-score | -0.23(-0.52, 0.07) | -0.49(-0.84, -0.16) | 0.23,0.23 | -0.22(-0.52, 0.09) | -0.48(-0.82, -0.15) | 0.23,0.23 |
|  |  |  |  |  |  |  |
| CBCL internalizing symptoms | 48.37(45.60, 51.13) | 48.40(45.09, 51.70) | 0.00,0.99 | 48.45(45.62, 51.28) | 48.29(45.12, 51.46) | 0.01,0.94 |
| CBCL externalizing symptoms | 49.37(46.58, 52.15) | 51.75(48.00, 55.50) | -0.20,0.30 | 49.48(46.45, 52.50) | 51.61(48.22, 55.00) | -0.18,0.35 |
| CBCL total symptoms | 48.20(45.54, 50.86) | 50.56(47.13, 54.00) | -0.21,0.27 | 48.29(45.45, 51.12) | 50.45(47.28, 53.62) | -0.20,0.32 |
| School-age assessment |
| KABC Sequential Processing | 80.52(77.96, 83.07) | 75.32(73.06, 77.60) | 0.57,<.01 | 80.59(78.22, 82.94) | 75.41(72.83, 78.00) | 0.57,<0.01 |
| KABC Planning | 78.83(75.47, 82.19) | 72.45(69.34, 75.56) | 0.53,<.01 | 78.58(75.50, 81.66) | 72.57(69.18, 75.95) | 0.50,0.01 |
| KABC Learning | 83.47(79.93, 87.01) | 77.53(74.43, 80.63) | 0.48,0.01 | 83.46(80.24, 86.68) | 77.34(73.80, 80.88) | 0.49,0.01 |
| KABC Simultaneous Processing | 82.40(78.32, 86.48) | 72.84(69.94, 75.73) | 0.71,<.01 | 82.00(78.53, 85.48) | 72.58(68.75, 76.40) | 0.70,<0.01 |
| KABC Mental Processing Index | 76.03(73.02, 79.05) | 69.96(67.52, 72.40) | 0.59,<.01 | 75.99(73.29, 78.70) | 69.89(66.92, 72.86) | 0.58,<0.01 |
|  |  |  |  |  |  |  |
| TOVA ADHD Index | -2.88(-3.61, -2.14) | -1.83(-2.90,-0.76) | -0.33,0.11 | -2.90(-3.77, -2.03) | -1.87(-2.80, -0.94) | -0.33,0.11 |
| TOVA percent omission errors | 25.37(20.08, 30.66) | 26.30(20.85) | -0.05,0.81 | 24.70(19.75, 29.66) | 26.89(21.60, 32.18) | 0.12,0.55 |
| TOVA percent commission errors | 11.96(8.94, 14.98) | 11.02(8.44, 13.60) | 0.090.64 | 12.00(9.22, 14.76) | 11.01(8.06, 13.96) | 0.10,0.63 |
| TOVA average response time speed (msec) | 763.70(723.90, 803.50) | 756.30(714.60,797.90) | 0.050.80 | 762.85(726.91, 798.78) | 763.89(725.57, 802.21) | -0.01,.90 |
| TOVA response time variability (msec) | 279.00(261.50, 296.50) | 267.30(247.10, 287.50) | -0.18,0.38 | 277.01(259.65, 294.36) | 269.10(250.36, 287.83) | -0.13,0.54 |
| TOVA signal detection D prime | 2.13(1.86, 2.40) | 2.10(1.86, 2.34) | 0.03,0.88 | 2.16(1.92, 2.40) | 2.08(1.83, 2.34) | 0.09,0.66 |
|  |  |  |  |  |  |  |
| CBCL internalizing symptoms | 57.78(55.36, 60.19) | 57.20(54.85, 59.56) | 0.060.74 | 57.84(55.55, 60.14) | 57.12(54.63, 59.62) | 0.08,0.68 |
| CBCL externalizing symptoms | 54.09(50.96, 57.21) | 56.16(52.69, 59.64) | -0.17,0.37 | 54.38(51.30, 57.44) | 55.81(52.48, 59.16) | -0.12,0.53 |
| CBCL total symptoms | 55.31 (52.79, 57.84) | 56.48(53.60) | -0.12,0.54 | 55.47(52.95, 57.60) | 56.28(53.51, 59.06) | -0.08,0.67 |

**Table 3.** Correlations of pre-school Malawi Developmental Assessment Tools (MDAT) total score (average standardized z score for Gross Motor, Fine Motor, Language/Hearing, and Social Development combined) with the school-age outcomes for the Kaufman Assessment Battery for Children (2nd edition) (KABC), Tests of Variables for Attention (TOVA), and Achenbach Child Behavior Checklist (CBCL). The correlations of pre-school MDAT with school-age CBCL are also presented at the bottom of the table.

|  |  |  |
| --- | --- | --- |
|  | **Control children** | **CM-R survivors** |
| **School-age outcome** | Correlation with MDAT, p-value | Correlation with MDAT, p-value |
| KABC Sequential Processing | 0.14.29 | 0.42<.01 |
| KABC Planning | -0.06.67 | 0.25.09 |
| KABC Learning | 0.09.49 | 0.32.02 |
| KABC Simultaneous Processing | 0.20.12 | 0.17.25 |
| KABC Mental Processing Index | 0.07.57 | 0.49<.01 |
|  |  |  |
| TOVA ADHD index | 0.12.37 | 0.20.18 |
| TOVA percent omission errors | -0.11.41 | -0.19.20 |
| TOVA percent commission errors | -0.12.36 | -0.16.30 |
| TOVA response time speed | -0.09.57 | -0.20.17 |
| TOVA response time variability | -0.27.05 | -0.23.13 |
| TOVA signal detection D prime | 0.17.23 | 0.21.15 |
|  |  |  |
| CBCL internalizing symptoms | -0.09 (.48) | -0.08 (.58) |
| CBCL externalizing symptoms | -0.31 (.02) | .01 (.94) |
| CBCL total symptoms | -0.21 (.11) | -0.08 (.59) |
|  | Correlation with pre-school CBCL, p-value | Correlation with pre-school CBCL, p-value |
| CBCL internalizing symptoms | 0.38 (<.01) | 0.17 (.24) |
| CBCL externalizing symptoms | 0.36 (<.01) | 0.51 (<.01) |
| CBCL total symptoms | 0.49 (<.01) | 0.56 (<.01) |

**Figure 1 Caption**

This figure depicts scatterplots for the Malawi Developmental Assessment Tools unadjusted average standardized *z* score total for the average of the four scales (Gross Motor, Fine Motor, Language/Hearing, Social), and the unadjusted Kaufman Assessment Battery for Children, 2nd Edition standardized Mental Processing Index scores. The upper plot is for the cerebral malaria children, and the lower plot is for the control children. The regression formula for the least-squares regression line is in the upper left corner for each plot, while the R-squared value is in the upper right corner.

