Published in final edited form as:

Pediatr Infect Dis J. 2014 August ; 33(8): 821–824. doi:10.1097/INF.0000000000000296.

Cerebral Malaria Retinopathy Predictors of Persisting Neurocognitive Outcomes in Malawian Children

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Abstract

Background—Neuropsychological sequelae from pediatric cerebral malaria (CM) have been well documented. Although malaria-specific retinopathy during acute illness has become a defining criterion for CM, its relationship to neurocognitive sequelae has not been documented. This relationship is important if malaria-specific retinopathy reflects the possible brain neuropathogenesis leading to long-term neurocognitive deficits.

Methods—From 2008 to 2012, 49 Malawian children 4.5 to 12 yrs of age surviving retinopathy-positive cerebral malaria (CM-R) were tested 1 to 3 yrs following illness with the Kaufman Assessment Battery for Children, 2nd edition (KABC-II), the Tests of Variables of Attention (TOVA), and the Achenbach Child Behavior Checklist (CBCL). In an observational study of a cohort of cerebral malaria survivors, these neurocognitive and behavioral outcomes were statistically related to types and severity of retinopathy measures, while controlling for age, sex, body mass index, socio-economic status, and time interval between illness and testing.

Results—Worse scores for hemorrhages, papilledema, optic disk hyperemia, retinal whitening of macula and foveal annulus were associated with poorer KABC-II mental processing index and global scale scores. Disk hyperemia was also predictive of TOVA D prime overall attention

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Disclosures. The authors have no financial relationships or conflicts of interest relevant to this article to disclose.

performance (inattention) and commission errors (impulsivity). Few associations were found between retinopathy scores and CBCL (emotional and behavioral) outcomes.

Conclusions—We are the first to report the relationship between severity of malaria-specific retinopathy during acute illness in CM survivors, and persisting neurocognitive problems. These findings support earlier studies documenting that severity of retinopathy during acute illness is medically prognostic in CM survivors. We extend these findings to include long-term neurocognitive outcomes.

Keywords

cerebral malaria; retinopathy; child neuropsychology; cognition; psychiatry

INTRODUCTION

Confirmed malaria-specific retinopathy is an important diagnostic consideration in cerebral malaria (CM) survivors. This is because almost one in four children with *P. falciparum* parasitemia who satisfy the standard clinical case definition of CM may have non-malarial etiologies for coma.¹ The identification of malarial retinopathy significantly improves diagnostic accuracy over standard clinical case definition in fatal cases, with 95% sensitivity and 100% specificity using autopsy findings as the gold standard.^{2, 3} However, even though severity of retinopathy is related to prognosis in CM children⁴ and immediate neurological sequelae following CM,^{5, 6} we know of no attempts to relate severity of retinopathy during acute illness to long-term neurocognitive or behavioral outcomes. This is the principal objective of the present study.

The retinopathy of severe malaria has three main components: retinal whitening; orange or white vessel discoloration (vascular abnormalities); and hemorrhages. Papilledema and disk hyperemia are also seen. However, these retina abnormalities are not specific for CM.² All of these retinopathy features are evaluated in each eye by an ophthalmologist using an indirect ophthalmoscope in children admitted to the pediatric ward in Blantyre Malawi (examination form available from the corresponding author upon request).⁷ We quantified these and other retinopathy domains for our CM study children and related these to neurocognitive and behavioral outcomes at 4.5 years of age and older.

METHODS

Study site and population

Queen Elizabeth Central Hospital is a tertiary referral center for a population of 533,000 people in Blantyre, Malawi. The participants in this study were eligible children from a larger exposure-control study designed to compare rates of epilepsy development in children who survived cerebral malaria who had retinopathy abnormalities when examined during acute illness (CM-R).⁸ We assessed 49 CM-R (26 males, 23 females) ranging from 5 to 12 yrs of age. Children with known HIV infection were excluded from our CM-R sample.

The CM-R children had been enrolled over a 3-year period prior to the initiation of this study, and were not tested with the present battery until they were at least 5 yrs of age.

Therefore the intervals between CM-R illness (median age of illness 3.6 yrs) and follow-up assessment were not uniform. The CM-R children in the present study were assessed from 1.33 to 6.50 years following the cerebral malaria illness ($mean = 3.87$ years, $SD = 1.66$), and time interval between illness and testing was controlled for in the analysis (Tables 1 – 3; Supplemental Digital Content Tables 1 through 3).

We obtained informed written consent from the parent or principal caregiver of each study child. Children 7 years of age or older provided written assent. IRB approval for this study was granted by Michigan State University and the College of Medicine for the University of Malawi. The informed consent process and the clinical evaluations were conducted using the local language, Chichewa, by Malawian research nurses fluent in that language.

Fundoscopy Retinopathy Examination at Hospital Admission for Cerebral Malaria

Retinal data was collected by a trained ophthalmologist using an indirect ophthalmoscope, to children admitted to hospital with a Blantyre coma score⁹ of less than or equal to 2 and a positive thick blood smear for *Plasmodium falciparum*. The exam can only be effectively performed on children when unconscious. The exam consisted of right and left eye evaluation for hemorrhages, papilledema, disk hyperemia, central retinal whitening in the macula and foveal annulus, peripheral whitening by eye quadrant (temporal, superior, inferior, nasal), and vascular abnormalities in the arteries/veins or capillaries which included orange or white discoloration. The examiner also noted the subjective overall severity of the retinopathy on a scale of 0 to 3+. Each of these domains was coded with an ordinal value with larger values indicating greater severity. The ordinal values for the right and left eye were combined as a summed score that captured changes in both eyes, and as a maximum score that captured the worst of the eyes. These scores for 8 retinopathy domains (hemorrhages, papilledema, disk hyperemia, whitening of the macula, whitening of the foveal annulus, sum of quadrant scores for peripheral whitening, number of quadrants with vascular change, and subjective severity score for total retinopathy) were related to neuropsychological and behavioral outcomes individually.

Kaufman Assessment Battery for Children, 2nd edition (KABC-II)

This test has been used to document persisting memory and other cognitive deficits in surviving cerebral malaria children in Senegal and in Uganda.^{5, 6, 10, 11} We utilized 13 individual sub-tests that generated neuropsychological global composite scores in Sequential Processing (memory), Simultaneous Processing (visual-spatial processing and problem solving), Planning (executive reasoning), and Learning.¹²

Test of Variables of Attention (TOVA)

The TOVA visual test (www.tovatest.com) is a continuous performance test of attention consisting of a smaller square presented rapidly within a larger square either in the upper position (signal) or lower position (non-signal). The child presses a switch in the preferred hand in response to the signal, and withholds responding to the non-signal. This test generates six visual performance indices that also capture dysfunction in attention and impulsivity that have proven sensitive to the effects of cerebral malaria in Senegalese and in Uganda children.^{6, 11, 13}

Achenbach Child Behavior Checklist (CBCL)

The school-age version of the CBCL (6 to 18 yrs) was translated into the local language independently by two individuals trained in psychology. Both versions were compared by the study team, led by MV, and discrepancies in translation reconciled by a consensus panel of two Malawian research nurses and a psychologist. The CBCL was administered to the principal caregiver in a separate room during the child's neurocognitive assessment.

Socio-economic status (SES)

Also at the time of neurocognitive assessment of the study child, the caregiver completed an SES questionnaire used in a previous developmental study of these cohorts.¹⁴ The SES questionnaire included a series of questions about parental status and educational and occupation, physical quality of home environment (e.g., type of toilet, roof, floor, electricity, water source), material possessions (e.g., mode of transportation, appliances, TV, radio), and food security.

Physical development

The weight, height, and mid-upper arm circumference (MUAC) of the child were measured before assessment, and these were standardized using the Epi Info WHO 2006 normative database for physical development.

Statistical methods

General linear models were used to relate the outcomes (KABC-II, TOVA and CBCL scores) to the scores for eight retinopathy domains. Each of the eight retinopathy domains was summarized from the sum of the scores for right and left eye, and as a maximum (worse) score for the two eyes. Ordinal explanatory variables with 4 or more categories were entered into the analysis as approximately continuous: hemorrhages (rated 0–4 for individual eye scores and 0–8 for the summed scores for right and left eye), whitening of the macula and foveal annulus (each rated 0–3 individually and 0–6 for the sum), sum of quadrant scores for peripheral whitening and number of quadrants with vascular abnormalities. Papilledema and disk hyperemia were rated as yes or no (coded as 1 or 0) for each eye, and the summed score for two eyes had 3 levels reflecting presence in none of the eyes, one eye, or both eyes. Subjective retinopathy scores were rated as 1, 2, or 3. Papilledema, disk hyperemia and subjective scores were entered into statistical models as categorical predictors of neurocognitive and behavioral outcomes. All models were adjusted for age, socioeconomic score, body mass index z-score, time interval between illness and testing. In addition, after excluding HIV-positive children from the study sample, the remaining sample contained 11 subjects with unknown HIV status. A dichotomous variable with 2 levels, known HIV-negative versus unknown status was entered as a covariate in the models. Its effects on the outcomes were not statistically significant, and analyzing the data only for those with known HIV-negative status did not change the magnitude of the statistical effects between neurocognitive outcomes and severity measures for the retinopathy domains. Therefore the final models included those with unknown HIV status but adjusted for HIV-negative versus unknown status in addition to other covariates.

RESULTS

Retinopathy in Right and Left Eye During Acute Illness

For hemorrhages, 38 out of 49 available values agreed for right and left eye. The agreement was perfect for disk hyperemia except for one missing value. For papilledema, 44 out of 47 available data points were in agreement for right versus left eye. The corresponding agreement figures were 41 out of 49 for whitening of the macula, and 39 out of 49 for whitening of the foveal annulus. These data explain why the results for retinopathy domain scores summed between two eyes and for the worse scores for the eyes were virtually the same. Therefore, the retinopathy domain scores were summed for right and left eye for the other tables relating those measures to the KABC-II (Table 1; Supplemental Digital Content Table 1), TOVA (Table 2; Supplemental Digital Content Table 2) and CBCL (Table 3; Supplemental Digital Content Table 3) outcomes. While summing the scores has a drawback of equating, for examples, scores of 2 and 0 for the two eyes with scores of 1 and 1, the summed score has an advantage of discriminating those with one eye affected versus both eyes. Simply using the worse score between the two eyes does not allow for this degree of quantitative precision in gauging severity of retinopathy for a given domain.

Retinopathy Measures during Illness as Predictive of KABC-II and TOVA Outcomes

The KABC-II Mental Processing Index (MPI) is a composite score of overall cognitive ability. This score was significantly associated with papilledema ($p<0.01$), disk hyperemia ($p=0.05$), whitening of the macula ($p=0.03$), and foveal annulus ($p<0.01$). While papilledema was predictive of almost all of the KABC-II global scale scores, the effects of whitening of the macular were statistically significant for the global domain of Simultaneous Processing (visual spatial memory and problem solving) ($p=0.02$); whitening of foveal annulus was associated with the global domains of Learning ($p=0.02$), and the domain of Planning (reasoning) ($p=0.02$). Sum of quadrant scores for retinal vascular discoloration, number of quadrants of vascular change in discoloration, and subjective overall retinopathy scores were not significantly associated with KABC-II global domain outcomes.

For TOVA scores, disk hyperemia was predictive of commission errors (impulsivity) ($p=0.01$) and D prime scores (signal detection performance of overall attention) ($p=0.04$). Other retinopathy domain scores were not significantly associated with TOVA scores, except for number of quadrants of vascular discoloration change being predictive of D prime ($p=0.04$). Given the number of statistical tests, this finding has limited strength of interpretation, as does the significant association of whitening of the macular with the CBCL conduct problems score ($p=0.04$). In contrast, the magnitude of the effects of retinopathy domain scores on KABC-II outcomes was consistently seen across the global scales of cognitive performance.

DISCUSSION

Because the retina and brain share many characteristics that may be relevant to the pathogenesis of pediatric cerebral malaria, malarial retinopathy may be a manifestation of the same mechanisms acting on other parts of the central nervous system to cause

neurocognitive sequelae.¹⁵ Like brain vessels, retinal vessels are subject to parasitized red blood cell sequestration, microvascular hemorrhage, immuno-pathogenic processes and compromise in the blood-brain barrier during severe malarial illness.¹⁶ Therefore, the features of retinopathy during CM offers an accessible and strategic vantage point in better understanding the pathophysiologic mechanisms associated with neurocognitive sequelae from CM.

We provide the first reported evidence that severity of retinopathy, especially papilledema, during acute cerebral malaria illness can be predictive of poorer cognitive performance years later. Central retinal whitening, disk hyperemia, and vascular discoloration abnormalities can also be predictive of poorer cognitive performance. However, our findings should be considered preliminary because we lacked an adequate sample size to provide a definitive profile of the specific retinopathy features most predictive of specific neurocognitive and behavior problem domains.

The severity of malarial retinopathy correlates with mortality and duration of coma in African children with cerebral malaria (CM). Most likely, retinopathy is related to the pathophysiology of the disease and is not an epiphenomenon.^{4, 16} Papilledema, a sign of raised intracranial pressure during the acute illness, was the feature most consistently associated with long-term cognitive deficits. Raised intracranial pressure may itself cause pervasive brain injury by impairing cerebral perfusion.

To illustrate, in a retrospective study of Senegalese children surviving cerebral malaria, Boivin (2002) documented significant deficits especially on KABC Simultaneous Processing (visual-spatial analysis and processing) as well as on Sequential Processing (visual and auditory working memory).¹¹ Boivin and colleagues (2007) documented KABC Sequential Processing deficits in CM survivors six months after illness in a prospective study of Ugandan children, although these findings were weaker at two-year follow-up.^{5, 6} With both the Senegalese and Ugandan school-age CM survivors, overall attention as measured by the TOVA was poorer compared to controls.^{5, 6, 11, 17} Likewise, KABC memory and TOVA attention measures were significantly lower for Ugandan CM children throughout two years following illness, when combined together in a neurocognitive deficit index.¹⁰ In the present study we observed significant relationships between features and severity of retinopathy during acute CM illness and persisting neurocognitive problems.

In addition, further work needs to be done to clarify the relationship between retinopathy severity and TOVA-based measures of attention in the aftermath of CM, as modified by other factors of clinical severity related to the pathophysiology of CM (e.g., hypoxic-ischemic versus immune-pathogenic mechanism of brain injury). In their review, Maude et al. (2009) suggest that retinopathy may correspond more closely to hypoxic-ischemic brain injury effects of CM, as opposed to pathophysiologic processes related to the breakdown of the blood-brain barrier in CM, or to cytokine inflammatory or nitric oxide levels in the brain.¹⁶ The retinopathy and corresponding clinical severity measures most significantly predictive of TOVA D Prime attention performance may represent metabolic and immune-pathogenic pathophysiologic features of acute illness, such as suggested by Marsh and colleagues (1996).¹⁸ Both TOVA and KABC-II neurocognitive outcomes have proven

sensitive to cytokine markers of immune-inflammatory aspects of CM in Ugandan children.¹⁹

The CM-R children in this present study were drawn from a large exposure/control study.⁸ A subset was evaluated with computerized axial tomography (CT) scan if they had persisting signs of neurodisability.²⁰ Some of these children had focal and multifocal lobar atrophy on CT that co-localized to regions of focal seizures during acute cerebral malaria. Clinical and sub-clinical brain damage of this sort from CM likely contributed to the high prevalence of emergent neuromotor and seizure disorders seen in the CM-R survivors in the parent study.⁸ This type of brain injury from CM may also disrupt neuropsychological functions of the sort observed in the present study, including working memory, visual-spatial processing and problem solving, and learning.^{20, 21} With the availability of MRI brain imaging technology now at the Blantyre Malaria Project site in Malawi, there is now the capability to relate the four principal types of retinopathy severity (hemorrhage, retinal whitening, papilledema, vascular abnormalities) to brain MRI structural abnormalities and corresponding persisting neuropsychological deficits. This is planned in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Michael J. Boivin, PhD, is Professor of Psychology and of Neurology/Ophthalmology at Michigan State University and served as study PI, wrote the grant proposals that funded this study, designed the study, developed the child assessment protocols, helped in the analysis of the data, and drafted the initial manuscript. Maclean Vokhiwa, MA, is a research coordinator with the Africa Mental Health Foundation and supervised the implementation of this study while serving as study coordinator with the Blantyre Malaria Project. He also supervised the child assessments and was responsible for the data management. Jed G. Magen, DO, is Associate Professor and Chair of the Psychiatry Department at Michigan State University and supervised the psychiatric screening assessments and the interpretation of these data, and helped design the study. Alla Sikorskii, PhD, is Associate Professor of Statistics and Probability at Michigan State University and completed all data analyses and tables and participated in the writing of the manuscript. Nicholas A.V. Beare, MD, is a lecturer with the Department of Ophthalmology at the Royal Liverpool University Hospital and completed many of the retinopathy exams and scoring, interpretation of the retinopathy findings in terms of pathophysiologic processes and neurocognitive outcomes, and participated in the writing of the manuscript. Michael J. Boivin and Alla Sikorskii had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study nurses Theresa Nnensa and Chimwemwe Kalenga assisted in the neurocognitive assessment of our study children, and administration of the CBCL to caregivers. We thank the study children and their caregivers from in and around Blantyre for their participation and support. This study is dedicated to them.

Funding Sources. This study was funded by the Michigan State University Department of Psychiatry (JGM), Department of Neurology and Ophthalmology faculty funding (MJB), and Office of the Vice President of Research and Graduate Studies award 07-IRGP-1060 (MJB). Funding support in the recruitment and clinical characterization of the study populations was provided by NIH R01 AI34969. The funding sources has no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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