MRI Findings in a Cohort of Brain Injured Survivors of Pediatric Cerebral Malaria

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Abstract. A prospective cohort study of retinopathy-confirmed cerebral malaria (CM) survivors identified 42 of 132 with neurologic sequelae. The 38 survivors with sequelae who were alive when magnetic resonance imaging (MRI) technology became available underwent brain MRIs. Common MRI abnormalities included periventricular T2 signal changes (53%), atrophy (47%), subcortical T2 signal changes (18%), and focal cortical defects (16%). The χ^2 tests assessed the relationship between chronic MRI findings, acute clinical and demographic data, and outcomes. Children who were older at the time of CM infection ($P = 0.01$) and those with isolated behavioral problems ($P = 0.02$) were more likely to have a normal MRI. Acute focal seizures were associated with atrophy ($P = 0.05$). Acute papilledema was associated with subcortical T2 signal changes ($P = 0.02$). Peripheral retinal whitening ($P = 0.007$) and a higher admission white blood cell count ($P = 0.02$) were associated with periventricular T2 signal changes. Chronic MRI findings suggest seizures, increased intracranial pressure, and microvascular ischemia contribute to clinically relevant structural brain injury in CM.

INTRODUCTION

The case fatality rate of pediatric cerebral malaria (CM) is 12–25%^{1,2} and ~30% of survivors experience neurological sequelae, including behavioral disorders, epilepsy, and developmental delay often with devastating neurologic deficits.³ Clinical risk factors for neurologic sequelae are higher maximum temperature, seizures, male gender, and a more profound coma at presentation.³ Aside from gross motor or functional deficits, many neurological sequelae are not apparent at discharge, but become manifest during more prolonged follow-up with directed history and assessment. To date, insights into central nervous system (CNS) structural abnormalities in pediatric CM have been largely limited to autopsy studies⁴ and a recent publication describing the acute brain magnetic resonance imaging (MRI) findings⁵ of CM. We set out to describe the follow-up brain MRI findings of pediatric CM survivors with neurologic sequelae from a previously published prospective cohort study.³ The MRI technology was not available at the time these children had their acute CM infection.

MATERIALS AND METHODS

Thirty-eight (38) brain-injured pediatric CM survivors, a subset† of a previously published prospective cohort study,³ underwent brain MRI at 6–24 months post sequelae identification. These CM survivors were prospectively enrolled and clinically characterized during their acute infection, including direct and indirect ophthalmoscopy through dilated pupils and serial electroencephalographs (EEG). Seizures were characterized according to clinical semiology and acute EEG findings. Prospective quarterly follow-ups were conducted to identify and characterize post-CM neurological sequelae.

Once MRI became available, MRIs were obtained on CM survivors in this cohort with neurologic sequelae using a 0.35T GE Signa Ovation magnet, with Sag T1, Ax Flair, Ax T2, and Ax diffusion weighted imaging sequences. Ethical approvals from the appropriate United States and Malawian institutional entities were obtained for the study and informed parental consent was required for this follow-up imaging.

Two radiologists interpreted the MRI images using a custom-designed computer program, NeuroInterp. NeuroInterp is a web-based program that requires interpreting radiologists to evaluate and quantify specific MRI findings (normal versus a scaled rating of any abnormality).⁶ Data were generated independently by two radiologists and NeuroInterp identified interpretations requiring adjudication based on predetermined criteria. Consensus reads were determined when adjudications were required. They were provided only with study subject's age and were therefore blinded to details of the sequelae.

An exploratory χ^2 analysis was carried out using the dichotomous outcome “any MRI abnormality” against “no abnormality” to assess possible associations between clinical characteristics and MRI abnormalities. We anticipated limited power for any analyses involving MRI findings with a frequency of < 15%, therefore any specific MRI abnormality seen in at least 15% of study subjects was also dichotomized and a similar analysis done. Given the exploratory nature of this analysis, no Bonferroni adjustment was made.

RESULTS

Among brain-injured CM survivors, 25 of 38 (66%) were male. The age range was 10–102 months (median 47 months). Neurological deficits indicative of CM-induced brain injury identified during follow-up included behavioral disorders in 12 (31.6%), developmental delay $\pm$ gross neurologic deficits in 23 (60.5%), and epilepsy in 9 (23.7%). Survivors frequently experienced multiple sequelae.

Brain MRI abnormalities were evident in 28 of 38 (74%) patients (see Table 1 and Figure 1). Abnormalities were generally seen in the cerebral hemispheres rather than the posterior

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†In the original cohort 42 children had neurologic sequelae but only 38 were still alive at the time of this follow-up imaging study.

TABLE 1
Clinical characteristics of brain-injured, cerebral malaria survivors (n = 38)

Clinical characteristic	Frequency	Normal vs. abnormal MRI (<i>P</i> value)
Demographics		
Gender (male)	25 (66%)	7/10 vs. 18/28 (<i>P</i> = 0.53)
Age in months (median, range)	38 (10–102)	Mean 54.6 vs. 32.4 (<i>P</i> = 0.014)
HIV + (<i>N</i> = 29)*	3 (10%)	1/8 vs. 2/21 (<i>P</i> = 0.67)
Complicated birth	2 (5%)	1/10 vs. 1/28 (<i>P</i> = 0.46)
Acute clinical		
Admit Blantyre Coma Score < 2	20 (66%)	6/10 vs. 19/28 (<i>P</i> = 0.47)
Admission hematocrit (mean % packed cell volume/μL)	18.7 (SD 5.0)	18.6 vs. 18.9 (<i>P</i> = 0.91)
Admission white blood cell (mean count/μL)	11,290 (SD 7,321)	7,633 vs. 12,857 (<i>P</i> = 0.05)
Hypoglycemia-documented at least once	19 (50%)	5/10 vs. 14/28 (<i>P</i> = 0.50)
Positive blood culture (<i>N</i> = 36)	6 (17%)	2/9 vs. 4/27 (<i>P</i> = 0.48)
Parasitemia (parasite/μL geometric mean)	58,202	49,985 vs. 42,052 (<i>P</i> = 0.69)
Lactate ≥ 5 (mean mg/μL) (<i>N</i> = 36)	21 (58%)	4/10 vs. 17/26 (<i>P</i> = 0.16)
Max temp (mean °C)	38.6 (SD 1.2)	38.6 vs. 38.7 (<i>P</i> = 0.79)
Focal seizures (by EEG, <i>N</i> = 31)	4 (13%)	1/8 vs. 3/23 (<i>P</i> = 0.27)
No EEG reactivity evident (<i>N</i> = 31)	14 (45%)	4/8 vs. 10/23 (<i>P</i> = 0.53)
Fundusoscopic findings		
Papilledema	12 (32%)	2/10 vs. 10/28 (<i>P</i> = 0.31)
Foveal whitening	33 (87%)	8/10 vs. 25/28 (<i>P</i> = 0.40)
Hemorrhage	21 (64%)	6/10 vs. 15/28 (<i>P</i> = 0.51)
Macular whitening	30 (91%)	8/10 vs. 22/28 (<i>P</i> = 0.65)
Peripheral whitening	27 (82%)	7/10 vs. 20/28 (0.61)
Outcome		
Behavioral disorder	12 (32%)	6/10 vs. 6/28 (<i>P</i> = 0.34)
Developmental delay†	23 (61%)	3/10 vs. 20/28 (<i>P</i> = 0.03)
Epilepsy	9 (24%)	2/10 vs. 7/28 (<i>P</i> = 0.05)

*Nine parents declined HIV testing.

†Including some with severe neurologic deficits.

MRI = magnetic resonance imaging; HIV = human immunodeficiency virus; EEG = electroencephalographs.

fossa. Common MRI abnormalities included periventricular T2 signal changes (53%) (Figure 1), generalized cerebral atrophy (47%) (Figure 2), subcortical T2 signal changes, which tended to extend throughout the deep white matter with relative sparing of the U fibers (18%) (Figure 3), and focal cortical defects (16%) (Figure 4). Abnormalities were less common in children with behavioral disorders compared with children with epilepsy and/or developmental delay (42% versus 68%; *P* = 0.02).

Table 2 details the MRI abnormalities seen and the findings of the exploratory analysis aimed at evaluating the association between acute clinical characteristics and demographic characteristics and chronic MRI abnormalities. Children who were older at the time of the acute CM infection were more likely to have a normal brain MRI. Seizures during CM (100% versus 44.4%; *P* = 0.05) and a higher admission white blood cell count (14,964 versus 8,075; *P* = 0.02) were associated

FIGURE 1. Periventricular white matter abnormalities (gliosis) Axial FLAIR (TR 2200, TE min full and FOV 25) and T2 frfse-xl (TR 3150, TE 125, and FOV 25).

FIGURE 2. Diffuse cerebral atrophy (Two levels of axial T2 frfse-xl and TR 3150, TE 125 and FOV 25).

with periventricular white matter changes. Two features of acute malarial retinopathy were associated with chronic brain MRI abnormalities. The presence of papilledema was associated with subcortical white matter changes (42% versus 8%; $P = 0.02$) and patients in whom peripheral retinal whitening was observed were more likely to have chronic periventricular white matter changes (63% versus 0%; $P = 0.007$).

In a *post-hoc* analysis, we compared children who experienced one type of sequelae to those with more than one type of sequelae to see if there were any differences in structural abnormality frequency. Nine of the 38 children experienced more than one type of sequelae. No significant differences in the frequency of structural abnormalities (any overall

abnormality or any specific abnormality) were identified (all P -values > 0.05).

DISCUSSION

This study offers insights into structural brain lesions evident on follow-up MRIs of pediatric CM survivors with very detailed acute clinical data as well as systematic long-term follow-up during which neurologic sequelae were evident. The primary limitations include the exploratory nature of the analysis, the absence of acute MRI data, the 0.35T MRI technology used, and the select nature of this group, which

FIGURE 3. Subcortical white matter changes (gliosis). Two axial T2 frfse-xl (TR 3150, TE 125, and FOV 25).

FIGURE 4. Focal cortical defect. Axial FLAIR (TR 2200, TE min full and FOV 25) and T2 frfse-xl (TR 3150, TE 125, and FOV 25).

included only children with neurologic sequelae and only those who survived to imaging.

Structural brain abnormalities were evident in nearly three-quarters of the CM survivors with neurological deficits. Focal seizures during CM, which were often multifocal, prolonged,

and refractory to treatment³ were associated with subsequent generalized cerebral atrophy. This atrophy may represent significant neuronal injury and subsequent neuronal death associated with prolonged seizures in the context of CM-associated metabolic challenges. Similar seizure frequency and severity

TABLE 2
Frequency of MRI findings at follow-up and acute clinical characteristics associated with these findings (*N* = 38)

MRI finding	Frequency of MRI finding*	Acute clinical characteristic associated with MRI finding†
Any abnormality	28 (74%)	Younger age at CM 32.3 vs. 54.6 months <i>P</i> = 0.01
Periventricular white matter changes	20 (53%) Usually < 25% of the area is involved	Admission WBC 14,964 vs. 8,075 <i>P</i> = 0.02 Peripheral retinal whitening 63% vs. 0% (<i>P</i> = 0.007) Acute focal seizures 100% vs. 44% (<i>P</i> = 0.05)
Atrophy	18 (47%) Diffuse 15 (39%) Hemispheric 2 (5%) Sulcal 1 (3%)	
Subcortical white matter changes	7 (18%) Always involves > 50% of the area	Acute papilledema 42% vs. 8% (<i>P</i> = 0.01)
Focal cortical changes	6 (16%)	None identified
Posterior fossa vs. supratentorial	Equal = 4 (11%) Predominantly supratentorial = 32 (84%) Predominantly posterior fossa = 2 (5%)	Not assessed‡
Posterior fossa abnormality	3 (8%)	Not assessed
Globus Pallidus T2 changes	3 (8%)	Not assessed
T2 cortical changes	3 (8%)	Not assessed
Frontal vs. posterior involvement	Equal = 2 (5%) Predominantly posterior = 35 (92.1%) Predominantly frontal = 1 (2.6%)	Not assessed
Caudate T2 changes	2 (5%)	Not assessed
Thalamus T2 changes	2 (5%)	Not assessed
Splenic predominance	2 (5%)	Not assessed
Putamen T2 changes	2 (5%)	Not assessed
Pontine T2 changes	1 (3%)	Not assessed
Mass lesion§	1 (3%)	Not assessed
Other	1 (3%)	Not assessed

*Not mutually exclusive.

†Evaluated for characteristics detailed in Table 1.

‡Not assessed for MRI findings that occurred in < 15% patients.

§Small granuloma.

MRI = magnetic resonance imaging; CM = cerebral malaria; WBC = white blood cell.

has been reported in a Kenyan CM population with routine EEG monitoring.⁷ Prolonged and recurrent seizures in the source population³ for this study and in Kenya⁷ are associated with a higher risk of neurologic sequelae. Intracranial pressure (ICP) monitoring in CM has shown ICP surges during seizures⁸ suggesting that larger studies could facilitate more complex, multivariate modeling to more fully elucidate the relationship between seizures, ICP, neurologic sequelae, and structural injury.

The exploratory analysis presented here also suggests a link between acute increased ICP, as evidenced by papilledema, and subsequent subcortical white matter gliosis. This appeared as a subtle graying of the subcortical white matter. It was generally diffuse throughout the peripheral deep white matter but had relative sparing of the U fibers. Previous autopsy-based studies have identified axonal injury as a key feature of CM⁹; the subcortical changes identified in the CM survivors with sequelae may represent axonal injury caused by increased ICP. Alternatively, axonal injury caused by impaired perfusion and/or other CM-mediated events, may lead to increased ICP. Serial acute imaging studies in CM are underway that may further elucidate the temporal order of events. The finding that increased ICP is associated with long-term structural abnormalities is also congruent with recent report that increased brain volume evident on MRI in acute CM predicts acute mortality.¹⁰

Peripheral retinal whitening, thought to be a manifestation of retinal ischemia caused by vascular obstruction from parasitized, sequestered red blood cells,¹¹ was associated with periventricular gliosis. This tended to be patchy but did have a predilection for the periventricular regions and provides further evidence that peripheral retinal whitening correlates to analogous brain ischemia likely from microvascular sludging and ischemia. As with other neurological conditions, funduscopy may be offering a "window" into the brain in CM. Prospective studies with acute serial brain MRIs, EEGs, and funduscopy examinations in children with CM are underway.

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