1.5 Tesla Magnetic Resonance Imaging to Investigate Potential Etiologies of Brain Swelling in Pediatric Cerebral Malaria

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Abstract. The hallmark of pediatric cerebral malaria (CM) is sequestration of parasitized red blood cells in the cerebral microvasculature. Malawi-based research using 0.35 Tesla (T) magnetic resonance imaging (MRI) established that severe brain swelling is associated with fatal CM, but swelling etiology remains unclear. Autopsy and clinical studies suggest several potential etiologies, but limitations of 0.35 T MRI precluded optimal investigations into swelling pathophysiology. A 1.5 T MRI in Zambia allowed for further investigations including susceptibility-weighted imaging (SWI). SWI is an ideal sequence for identifying regions of sequestration and microhemorrhages given the ferromagnetic properties of hemozoin and blood. Using 1.5 T MRI, Zambian children with retinopathy-confirmed CM underwent imaging with SWI, T2, T1 pre- and post-gadolinium, diffusion-weighted imaging (DWI) with apparent diffusion coefficients and T2/fluid attenuated inversion recovery sequences. Sixteen children including two with moderate/severe edema were imaged; all survived. Gadolinium extravasation was not seen. DWI abnormalities spared the gray matter suggesting vasogenic edema with viable tissue rather than cytotoxic edema. SWI findings consistent with microhemorrhages and parasite sequestration co-occurred in white matter regions where DWI changes consistent with vascular congestion were seen. Imaging findings consistent with posterior reversible encephalopathy syndrome were seen in children who subsequently had a rapid clinical recovery. High field MRI indicates that vascular congestion associated with parasite sequestration, local inflammation from microhemorrhages and autoregulatory dysfunction likely contribute to brain swelling in CM. No gross radiological blood brain barrier breakdown or focal cortical DWI abnormalities were evident in these children with nonfatal CM.

INTRODUCTION

Pediatric cerebral malaria (CM), defined as *Plasmodium falciparum* peripheral parasitemia and unarousable coma with no other coma etiology evident, primarily affects children in sub-Saharan Africa.¹ Although antimalarial agents provide rapid parasite clearance, mortality rates remain high (8–25%).^{2,3} The pathological hallmark of pediatric CM at autopsy is intravascular sequestration in which parasitized red blood cells (RBCs) adhere to the endothelium of cerebral microvessels.

Although malaria causes almost a million deaths per year, neuroimaging capacity is typically limited in malaria-endemic regions. Only one large magnetic resonance imaging (MRI) case series from Malawi using a 0.35 Tesla (T) MRI has provided insights into the in vivo structural abnormalities associated with pediatric CM⁴ and CM mortality.⁵ Other studies and case reports using higher field MRIs have been performed primarily on adults with few children included,^{3,6,7} but adult CM appears to represent a different disease syndrome.⁸ In adult CM, coma onset largely occurs some days after illness onset in the setting of multisystem organ failure often including hepatic dysfunction, renal failure, and gross electrolyte abnormalities. As such, the coma of adult CM is clinically

dominated by the effects of a toxic, metabolic encephalopathy. By contrast, in pediatric CM coma onset occurs very early in the malaria illness, often as one of the first signs of the illness, with very limited hepatic or renal involvement and no evident systemic cause for coma. Most MRI insights gained from imaging pediatric CM to date have been limited to low-field MRI technology.

A recent pediatric CM MRI study used 0.35 T technology to establish that increased intracranial pressure due to increased brain volume is the cause of death in CM,⁹ but the low-field MRI technology was unable to further evaluate the potential etiologies of brain swelling in pediatric CM, so the underlying cause(s) of cerebral edema in CM remains unclear. Further study delineating the underlying cause(s) of swelling is needed to develop appropriate interventions. Potential etiologies suggested by autopsy and clinical studies include any/all of the following: 1) blood brain barrier (BBB) breakdown with resultant vasogenic edema^{10,11}; 2) cytotoxic edema associated with cell death¹²; 3) vascular congestion due to occlusion at the post-capillary venules¹³; 4) hyperemia with autoregulatory dysfunction due to endothelial injury and CM-associated seizures, anemia, and hyperpyrexia^{14–16}; and 5) diffuse cerebral microhemorrhages (i.e., ring hemorrhages).¹¹

Hemozoin is an iron-rich breakdown product of the parasite's metabolism of hemoglobin.⁵ Hemozoin is present primarily in mature, sequestered parasites. Thus, susceptibility-weighted imaging (SWI),¹⁷ which is extremely sensitive to the magnetic field inhomogeneity caused by ferromagnetic substances, is an ideal imaging sequence for identifying regions of parasite sequestration. SWI also offers the ability to identify small

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hemorrhages on the order of several microgram of blood per gram of tissue.^{18,19}

We hypothesized that imaging retinopathy-confirmed pediatric CM with a 1.5 T MRI including diffusion weighted imaging (DWI), SWI, and gadolinium-enhanced sequences would identify pathophysiological mechanisms underlying cerebral edema in pediatric CM and undertook an imaging study of CM in Zambia where 1.5 T MRI is available specifically seeking evidence of BBB breakdown, cytotoxic edema, parasite sequestration, autoregulatory dysfunction, and microhemorrhages.

MATERIALS AND METHODS

Subjects and recruitment. During the malaria seasons (January–June) in 2012–2014, comatose children with retinopathy-confirmed²⁰ CM underwent brain MRI on the 1.5 T MRI scanner (Siemens Magnetom Essenza using Syngo MR 200 4A version software; Siemens Global, Erlangen, Germany) at the Cancer Diseases Hospital in Lusaka, Zambia, within 24 hours of admission. Inclusion criteria were 1) admission to the pediatric high care unit of the University Teaching Hospital, 2) a Blantyre Coma Score of ≤ 2 ,²¹ 3) *P. falciparum* infection as determined by a Paracheck Rapid Diagnostic Test, 4) the presence of malarial retinopathy, and 5) no other evident etiology for coma. A thick peripheral blood smear to identify parasitemia was also obtained before recruitment, but was not immediately available and was not required for inclusion. All children received standard antimalarial treatment, anticonvulsants, antipyretics, antibiotics, and blood transfusions, as clinically indicated and in accordance with national treatment guidelines. As per present treatment standards, no steroids were given. Children with comorbid meningitis as determined by cerebrospinal fluid analysis were excluded from enrollment. Written consent was obtained from the child's parent or guardian. Children with impaired renal function (creatinine ≥ 2.0) did not receive gadolinium. This study was approved by the Institutional Review Boards at the University of Zambia, Michigan State University, and the University of Rochester.

Imaging. Gadolinium (Magnevist) doses were determined by individual patient weight and administered intravenously (0.2 mL/kg, 0.1 mmol/kg) by hand injection. The scanning protocol is provided in an appendix. Apparent diffusion coefficient (ADC) calculations were provided by the standard Siemens software algorithms.²² SWI phase images were collected unfiltered and postprocessed with a 64 × 64 high pass filter then viewed using signal processing in nMR (SPIN) software. SWI was also collected with a shorter echo time (15 ms) for some subjects to avoid potential aliasing.¹⁷

Interpretation. Images were reviewed independently by two radiologists (MJP; neuroradiologist, and SDK; MRI fellowship trained radiologist) and data were managed using NeuroInterp, a web-based program that allows radiographic findings to be entered into a searchable and quantified database.²³ Reader discrepancies, determined in advance of the analysis, were reevaluated by the two radiologists to develop a consensus interpretation.

Increased brain volume, the imaging finding associated with fatal CM, was rated on a scale from 1 to 8 with three being no edema and one and two indicating atrophy. An edema score of 4 to 5 indicated minimal–mild edema, with no loss of sulcal markings. Grade 6 (moderate edema) was defined as loss of

some sulcal markings. An edema score of 7 represented moderate/severe edema with diffuse sulcal and cisternal effacement universally evident but without herniation present, and the severe edema score of 8 required sulcal and cisternal effacement with evidence of herniation.

MRI findings coded within the NeuroInterp database that could plausibly be associated with the five potential pathogenic mechanisms of brain swelling in CM were then reviewed. Specifically, 1) to evaluate gross BBB breakdown causing vasogenic edema, we looked for evidence of gadolinium enhancement,²⁴ 2) to assess for cytotoxic edema, we looked for edematous regions with gray matter DWI abnormalities,²⁵ 3) evidence for vascular congestion or venous micro-occlusion was sought by looking for white matter DWI abnormalities,²⁶ 4) autoregulatory dysfunction was evaluated by looking for focal regions of symmetric hemispheric edema of varying confluence in regions susceptible to autoregulatory vulnerabilities,^{9,27} and 5) SWI abnormalities were assessed clinically and quantitatively based on effective voxel susceptibility with the anticipation that these would be located in the same anatomical regions as ring hemorrhages and sequestration have been identified in prior autopsy studies.²⁸ Given the small anticipated sample size (< 20 subjects) and the lack of a normal control group, no statistical analyses or comparisons were planned.

RESULTS

Patient characteristics and data acquisition. Twenty-three children met the study inclusion criteria during the enrollment period. Parents declined participation for two children, and five children were deemed too ill to transfer for imaging or died before imaging could be performed, so 16 subjects were imaged—5 (31%) were male and the mean age was 6.4 years (range 1–15). Table 1 provides demographic data and admission clinical characteristics from the 16 subjects who were imaged.

Of the five consented children who were not imaged, three died. Among the 16 subjects imaged, the scans for one patient were nondiagnostic on the SWI sequence due to movement artifact. Renal function could not be ascertained on two children, so these subjects did not receive gadolinium. There were no fatalities among the imaged study subjects and none had clinical sequelae evident at discharge. Table 2 provides the frequencies of the 1.5 T MRI findings identified and captured in NeuroInterp.

MRI findings. Increased brain volume. None of the subjects had severe (grade 8) edema. Moderate/severe (grade 7) edema was present in 2/16 (13%); moderate (grade 6) edema in 4/16 (25%); minimal/mild (grade 4 and 5) edema in 7/16 (44%); and no edema in 3/16 (19%).

T2 signal changes. The total number of cases exhibiting white matter increased T2 signal was 12/16 (75%), and two distinct patterns were observed: primarily subcortical (10/12, or 83%) and primarily periventricular/peritrigoneal (2/12, 17%) (Figure 1). These generally occurred in isolation; only two cases had both findings.

Gadolinium enhancement. The expected normal physiological intravascular and circumventricular organ enhancement was evident in all subjects on the post-contrast images (Figure 2). A small region of subtle focal cortical enhancement was seen in one subject with positive SWI signal and no

TABLE 1
Demographic and admission clinical characteristics

Subject	Age (months)	Gender	Glucose (mmol/L)	Lactate (mmol/L)	Seizures before admission	Fever duration before admission (days)	Coma duration before admission (days)	Antimalarial received before admission
1	75	Male	7.3	5.9	None	2	1	None
2	187	Female	9.3	7.1	Focal	6	2	Quinine
3	57	Female	3.7	10.0	None	3	1	None
4	34	Female	8.6	10.2	Generalized	2	0.5	LA
5	147	Male	4.3	7.3	Generalized	3	1	LA
6	98	Female	3.3	7.2	Generalized	3	1	LA
7	157	Male	2.9	7.6	Generalized	4	2	LA
8	12	Male	3.3	6.0	Generalized	5	2	LA
9	42	Female	4.3	6.5	Focal	7	4	LA Quinine
10	51	Male	4.1	8.1	Generalized	4	2	Quinine
11	31	Female	4.1	6.2	Generalized	4	2	Quinine
12	53	Female	5.3	8.4	Generalized	3	1	LA
13	62	Female	4.8	6.2	None	4	1	None
14	123	Female	4.1	7.6	Generalized and focal	6	0.5	LA
15	18	Female	5.2	8.1	Focal	3	0.5	None
16	82	Female	6.0	4.2	Generalized	2	1	None

CM = cerebral malaria; LA = artemether-lumefantrine.

associated T2 abnormalities consistent with a capillary telangiectasia. There was no evidence of gadolinium extravasation in the other 13 patients who received contrast.

Cortical findings. Cortical swelling and increased T2 signal was seen in 10/16 (63%), but these signal abnormalities were relatively mild in extent, confluent, and without associated cortical DWI findings. Increased cortical T2 signal was generally diffuse, with only 2/16 (13%) having a posterior predominant pattern.⁴ DWI showed restricted water diffusion in the subcortical white matter in 10/16 (63%) which was confirmed by accompanying ADC maps.

Basal ganglia and thalamus abnormalities. The structures in the basal ganglia had different levels of involvement. T2/fluid attenuated inversion recovery signal abnormalities were present in the globus pallidus and putamen in 10/16 (63%), and the caudate in 9/16 (56%). Although frequently involved simultaneously, there was generally a region of predominance (Figure 3). Regional differences were also illustrated in the DWI images. Fifty-six percent of the subjects had DWI abnormalities in the globus pallidus, 13% in the putamen, and none in the caudate.

Pontine and brainstem signal abnormalities. This was assessed at two levels, within the pons at the level of the middle cerebellar peduncle and within the brainstem at the level of the substantia nigra. Pontine involvement was seen in 9/16 (56%) and brainstem in 11/16 (69%). Abnormalities were usually diffuse and consisted of generalized increase in T2 signal. However, focal areas of involvement were also seen.

Corpus callosum. It showed increased T2 signal and thickening in 10/16 (63%) with 6/10 having associated positive DWI findings as confirmed by ADC maps. The splenium was the primary site of involvement in 9/10 (90%) cases.

SWI findings. Decreased signal is defined as a positive SWI finding as it localizes to areas of magnetic field inhomogeneity caused by the presence of a ferromagnetic substance (Figure 4). SWI findings were noted along the regions of the venules of both the superficial and deep venous systems corresponding to areas of parasite sequestration and ring hemorrhages. SWI resolution did not allow distinction between gray and white matter involvement in the cerebellum. One SWI dataset was not interpretable because of severe motion artifact. In the remaining cases, 7/15 (47%) showed

abnormal paramagnetic signal within the following regions of the parenchyma: corpus callosum (7/15, 47%), subcortical white matter (6/15, 40%), cerebellum (5/15, 33%), lenticulae striate (5/15, 33%), and periventricular white matter (2/15, 13%). In two subjects, both the internal capsule and optic radiation had abnormal paramagnetic signal.

The susceptibility of heavily infected RBCs is ~1,880 parts per billion (ppb) relative to water.¹⁸ The effective voxel susceptibilities in the corpus callosum and junction of the cortical gray and white matter was 50 ppb relative to water in susceptibility weighted imaging and mapping. As distributed within the voxel, this represents a 1/38th decrease in susceptibility. Given the voxel size of $0.5 \times 0.5 \times 2.0 \text{ mm}^3$, this represents 1/78th μL . Assuming the capillary volume is ~5% (or 1/20th of the pixel),²⁹ this indicates that approximately half of the capillaries are filled with hemozoin.

The combination of moderate to severe symmetrical cortical swelling (edema score of 6 or 7), with corresponding

TABLE 2
The frequency of 1.5 T MRI findings of pediatric CM (N = 16)

MRI finding at 1.5 T
Moderate/severe edema, 2 (12%)
Gadolinium enhancement (N = 14), 0
SWI findings/ring hemorrhages and/or sequestration (N = 15), 7 (44%)
White matter T2 abnormalities, 12 (75%)
White matter DWI abnormalities, 10 (63%)
T2 cortical abnormalities, 10 (63%)
Cortical DWI abnormalities, 0
Pontine T2 changes, 9 (56%)
Brainstem T2 changes, 11 (69%)
Globus pallidus T2 changes, 10 (63%)
Globus pallidus DWI abnormalities, 9 (56%)
Putamen T2 changes, 10 (63%)
Putamen DWI abnormalities, 2 (13%)
Caudate T2 changes, 9 (56%)
Caudate DWI abnormalities, 0
Thalamic involvement, 6 (38%)
Corpus callosum T2 abnormalities, 10 (63%)
Corpus callosum DWI abnormalities, 6 (38%)
Predominantly splenial involvement, 4 (66%)
Posterior fossa DWI changes, 1 (6%)
Posterior fossa signal abnormalities, 6 (38%)
Preexisting abnormality, 1 (6%)

CM = cerebral malaria; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging; SWI = susceptibility-weighted imaging.

FIGURE 1. The finding of vasogenic edema demonstrated by isolated white matter T2/fluid attenuated inversion recovery (FLAIR) signal changes encompasses multiple potential etiologies for brain swelling. Two distinct types of white matter changes seen in pediatric cerebral malaria are seen on the 1.5 Tesla (T) MRI based in Zambia. They appear as areas of increased (bright) signal on (A) T2 2D SE TR 3400 TE 85 slice thickness 4/0 matrix 256×192 and (B) FLAIR IR with TR 9000 TE 130 TI 220 slice thickness 4/0 matrix 256×192 (curved arrows), illustrated in a 4-year-old female. The image shows a subcortical distribution with involvement of the u-fibers and sparing of the deep white structures. The other type, as illustrated on (C)-T2 2D SE TR 3400 TE 85 slice thickness 4/0 matrix 256×192 and (D)-FLAIR R with TR 9000 TE 130 TI 220 slice thickness 4/0 matrix 256×192 (open curved arrows), is seen in a 3-year-old female with images demonstrating a periventricular distribution, predominately in the peritrigoneal regions. This figure appears in color at www.ajtmh.org.

underlying subcortical white matter changes with associated DWI and ADC findings was evident in 4/16 (25%) of cases (Figure 5) with two of the four showing a predominantly posterior distribution.

Table 3 summarizes the MRI findings seen using 1.5 T in 16 Zambian children with CM in the context of the proposed mechanisms for brain swelling in CM and the 1.5 T MRI findings anticipated for each mechanism.

DISCUSSION

MRI findings using a 0.35 T MRI have shown that death from pediatric CM occurs because of increased brain volume,⁹ but low field MRI was unable to further delineate the etiology for

the brain swelling. Intervention studies aimed at reducing or preventing cerebral edema in CM would ideally target the underlying mechanism of swelling. Existing clinical and autopsy data suggest at least five potential etiologies for brain swelling in CM. In this study, we describe what the MRI findings associated with each of these potential etiologies would be and then used 1.5 T MRI in children with retinopathy-confirmed CM to identify the presence or absence of findings consistent with each of the five proposed etiologies. As such, the results of this study can be subdivided into evidence both for and against these specific potential origins of brain swelling in pediatric CM.

Decreased SWI signal was evident on the brain MRIs of children with CM, and furthermore these changes were seen in

FIGURE 2. The capillary walls of the cerebral blood vessels are of continuous type with tight junctions and a continuous basement membrane which forms the blood brain barrier (BBB). It provides a physical resistance to the passage of lipophilic substances from the cerebral capillaries into the extravascular spaces. Gadolinium, a lipophilic magnetic resonance imaging contrast agent, does not cross an intact barrier. Following contrast administration, normal expected intracranial contrast enhancement can be seen within the vascular structures such as the arteries (A, yellow arrow) and veins (A, red arrow), cavernous sinuses (B, curved arrows), and in the limited circumventricular organs which have fenestrated basement membranes, and therefore, lack a BBB, such as the pituitary (B, vertical arrow) and choroid plexus (C, two headed arrow) as seen on these postcontrast T1-weighted images (TR-TE) in this 5-year-old female with cerebral malaria (CM). The lack of gross extravasation into other areas of the brain in this population of pediatric CM patients is indicative of an intact BBB. This figure appears in color at www.ajtmh.org.

FIGURE 3. Deep venous obstruction tends to have focal areas of involvement. This includes the basal ganglia. Classical basal ganglia lesions were seen (arrows) and frequently had regional predominance in pediatric cerebral malaria such as seen in this 3-year-old female (A) T2 2D SE TR 3400 TE 85 slice thickness 4/0 matrix 256×192 and (B) fluid attenuated inversion recovery (FLAIR) 2D FLAIR IR with TR 9000 TE 130 TI 220 slice thickness 4/0 matrix 256×192 having disproportionate signal changes in the Globi Pallidi. Similar findings are also seen to a somewhat lesser extent in this 4-year-old male (C) T2 2D SE TR 3400 TE 85 slice thickness 4/0 matrix 256×192 and (D) FLAIR 2D FLAIR IR with TR 9000 TE 130 TI 220 slice thickness 4/0 matrix 256×192 . Note that the involvement is primarily along the posterior medial margin. This figure appears in color at www.ajtmh.org.

regions where prior autopsy studies have shown micro-hemorrhages (Figure 6) as well as in the regions where sequestration is common. Because the SWI signal effectively identifies blood products and hemozoin, both sequestration and ring hemorrhages were likely identified. Marked T2/DWI abnormalities were evident in the subcortical brain regions most sensitive to venous outflow obstruction. If perfusion is obstructed in regions with SWI signal changes, then blood

flow to the tissue would decrease by $\sim 50\%$ which is consistent with what is seen in an animal model of malaria where blood flow was found to be reduced to $53\% \pm 12\%$.²⁹

In the setting of the sequestration-associated SWI abnormalities and intact large venous drainage systems (i.e., no venous thrombosis), the T2/DWI findings are strongly suggestive of a venous obstruction phenomenon in the capillary bed system. Much of what is known about pediatric CM has

FIGURE 4. Abnormal susceptibility-weighted imaging (SWI) signal is shown as dark signal within the structure indicating an increase in paramagnetic susceptibility. SWI (3D SWI TR 9500 TE 110 TI 2000 slice thickness 4/0 matrix 512×256) phase comparing subjects with normal appearing brain tissue (A–C) and those with abnormal findings (D–F) in SWI. The splenium and genu of the corpus callosum (A, D), the junction of cortical gray matter and subcortical white matter (B, E), and cerebellum (C, F) are shown and labeled.

FIGURE 5. Autoregulatory dysfunction is demonstrated by cortical swelling with underlying white matter changes shown by increased T2 and diffusion-weighted imaging (DWI) signals. These findings are shown in this 6-year-old female with cerebral malaria. Although the cortical swelling is mild in this case, the underlying subcortical white matter changes (arrows), including increased (bright) T2/fluid attenuated inversion recovery (FLAIR) signal on (A) T2 2D SE TR 3400 TE 85 slice thickness 4/0 matrix 256×192 and (B) FLAIR 2D FLAIR IR with TR 9000 TE 130 TI 220 slice thickness 4/0 matrix 256×192 as well as the associated restricted water movement (diffusion), as demonstrated by increased (bright) DWI signal (C) DWI TR 9000 TE 70 slice thickness 5/0 matrix 132×128 and decreased (dark) apparent diffusion coefficients (ADC) signal (D) DWI TR 9000 TE 70 slice thickness 5/0 matrix 132×128 and is the ADC are evident. These findings in this child who rapidly and fully recovered clinically are consistent with posterior reversible encephalopathy syndrome, although repeat imaging was not obtained to confirm reversibility of the structural abnormalities. This figure appears in color at www.ajtmh.org.

been learned from autopsy studies, so it is reassuring to see that the distribution of microhemorrhages and parasite sequestration found in prior autopsy studies are very similar in distribution to the microhemorrhages and parasite sequestration identified in living children who survived CM.

Vasogenic edema was demonstrated by increased T2 signal in the white matter. Cytotoxic edema has a similar appearance, but is accompanied by restricted water motion and increased DWI signal in the gray matter which was not seen in this group of pediatric CM patients. None of these children died and there were no clinical sequelae at discharge, also consistent with a reversible process.

MRI findings of symmetrical cortical swelling with underlying white matter changes were seen in children who fully and rapidly recovered. This is clinically consistent with posterior reversible encephalopathy syndrome (PRES) and suggests an underlying autoregulatory dysfunction. Although we do not have repeat imaging to confirm reversibility of the structural lesions, the children with PRES-like findings fully

and completely recovered during the brief acute admission which provides some significant evidence of reversibility. When caring for patients with PRES, repeat imaging is seldom undertaken if clinical recovery is complete and the radiographic diagnosis of "PRES" is generally given at the time of acute imaging (i.e., not after subsequent imaging).

PRES has been previously reported in CM³⁰ and pediatric CM is clinical congruent with many other clinical conditions associated with PRES. Specifically, pediatric CM generally involves a rapid neurologic deterioration, usually in the setting of seizure, followed by relatively prompt full recovery in most patients. Radiographically, brain swelling with underlying vasogenic edema associated with positive DWI findings is the hallmark of both CM and PRES.^{4,16} Autoregulatory dysfunction as a result of the primarily endothelial process associated with parasite sequestration in CM may result in vasoconstriction coupled with hypoperfusion causing vasogenic edema and associated brain swelling. This is the favored theory for the etiology of the radiographic findings seen in PRES.²⁷

TABLE 3
1.5 T MRI findings in the context of proposed etiologies of increased brain volume

Potential etiology for increased brain volume in pediatric CM	1.5 T MRI findings anticipated for this etiology	Findings in Zambian children with nonfatal CM (1.5 T, N = 16)
Blood brain barrier breakdown Impaired perfusion causing cytotoxic edema	Gadolinium enhancement ³² Gray matter increased DWI signal. ²⁵	No gadolinium enhancement No increased DWI signal in gray matter.
Vascular congestion/venous micro-occlusion	White matter increased DWI signal ²⁶	Subcortical white matter changes with corresponding increased DWI signal/ (ADC) abnormalities in border zone distribution
Hyperemia/autoregulatory dysfunction	Focal regions of symmetric hemispheric edema identified via increased T2 and increased DWI signals that are confluent with more severe edema ^{9,16}	Symmetric cortical thickening with increased T2 signal. Underlying white matter T2/FLAIR & DWI (ADC) changes
Ring hemorrhages with local inflammation and/or local sequestration	SWI-positive findings in the subcortical white matter, corpus callosum, basal ganglia, and both gray matter and/or white matter in the cerebellum ²⁸	SWI findings correlating to expected areas of hemorrhagic distribution. Associated T2/FLAIR signal changes in similar regions.

ADC = apparent diffusion coefficients; CM = cerebral malaria; DWI = diffusion-weighted imaging; FLAIR = fluid attenuated inversion recovery; MRI = magnetic resonance imaging; SWI = susceptibility-weighted imaging.

FIGURE 6. Gross pathologic image of a typical brain at autopsy (**A**) from a fatal pediatric patient (not from a participant in this study) demonstrates the presence of petechial hemorrhages in the white matter (black arrows, left half of image). If the cortical ribbon is demarcated from the white matter (blue line, right half of image), it is clear that the hemorrhages are restricted to the subcortical and deep white matter. Also note the swollen gyri. This correlates well with the in vivo magnetic resonance imaging (MRI) images seen specifically as low signal (arrows) on (**B**) susceptibility-weighted imaging (SWI) (3D SWI TR 9500 TE 110 TI 2000 slice thickness 4/0 matrix 512 × 256) and high signal (arrows) on (**C**) fluid attenuated inversion recovery (FLAIR) (2D FLAIR IR with TR 9000 TE 130 TI 220 slice thickness 4/0 matrix 256 × 192) of an 8-year-old female with cerebral malaria (CM). The dark signal on the SWI sequence is the result of increased ferromagnetic substances associated with parasite sequestration and micro-hemorrhages which causes magnetic field inhomogeneity and MRI signal loss.

No other potential etiologies for PRES were identified in this population. None of the participants had received any medications known to induce PRES before imaging. All were normotensive and sickle-cell negative. Renal function was normal in 14/16 who underwent creatinine testing, and the two who did not undergo testing had no clinical signs of renal failure. More extensive metabolic assessments were not available.

We found no evidence of cortical cytotoxic edema and there was no radiographic evidence of gadolinium enhancement, although gadolinium was clearly seen within the vessels and in circumventricular organs. Gadolinium, as a contrast agent, is chelated by a range of very small molecules (Magnevist 0.54 kDa).³¹ These agents are all hydrophobic, so they do not cross the intact BBB. At autopsy in CM, areas of sequestration show fibrinogen (340 kDa)²⁴ leakage and ring hemorrhages which require sufficient BBB breakdown to allow a deformable, non-parasitized blood cells (7 μ M) to escape. The SWI imaging in this study identified ring hemorrhages, so some BBB breakdown associated with their presence must have occurred, but if there was associated gadolinium extravasation, the quantity and concentration of gadolinium was insufficient to be visually evident on MRI. Gross BBB breakdown indicative of severe vasogenic edema was not evident in this small series of nonfatal pediatric CM.

This study is limited by the small sample size, a preponderance of less severe edema spectrum, and lack of a comparison group. In Zambia, children felt to be at risk of imminent death were not imaged because this requires ambulance transportation to an adjacent facility. The small number of subjects prevented meaningful quantitative analyses despite the use of NeuroInterp. Although no a priori analyses were planned, we did conduct a post hoc comparison to determine if the edema score or the presence of SWI, DWI, or focal cortical abnormalities was associated with age, coma duration before admission, or seizures before admission. No associations were found (all P 's > 0.05). The absence of subjects with severe brain swelling (edema score of 8) or fatal disease may have impacted our findings, as florid BBB breakdown might not occur to a significant degree in less severe CM swelling. Normal MRIs on a similar aged

comparison group were not available. In the Zambian setting, most imaging is obtained on advanced disease with normal images being uncommon. Acquisition of imaging in an age-comparable group of healthy children was not feasible given the risk of sedation, particularly in this environment. Finally, more quantitative MRI analyses would have allowed more optimal assessments, but the power injections equipment required to obtain perfusion studies and/or dynamic contrast enhanced studies, which could detect contrast influx too small to be visually evident, is prohibitively expensive and was not available in this resource limited setting. Better resolution and quantitative data would have been possible with the use of an automated pressure injector, but BBB breakdown of the magnitude that is seen in conditions such as meningitis or brain tumors was clearly not present as these conditions are well recognized for demonstrating gadolinium extravasation with gadolinium hand delivery.

CONCLUSIONS

Pediatric CM brain MRI findings in nonfatal cases using 1.5 T technology suggest that vascular congestion, autoregulatory dysfunction, and microhemorrhages likely contribute to brain swelling pathogenesis.

Received April 12, 2017. Accepted for publication November 14, 2017.

Published online January 8, 2018.

Acknowledgments: The University Teaching Hospital's Neurology Research Office (UTH NRO) with its exceptional staff provided critical administrative support for this work. We also thank the University of Rochester for supporting UTH NRO and the Cancer Diseases Hospital for support in conducting research-level MRIs. Finally, we are also grateful to the families who agreed to participate in this study and to the many clinicians and nurses who cared for the study participants.

Financial support: This work was supported by the Dana Foundation's Program in Brain and Immuno-Imaging (M. J. P.).

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REFERENCES

- WHO, 2011. *World Malaria Report*. Geneva, Switzerland: World Health Organization.
- Dondorp AM et al., 2011. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 376: 1647–1657.
- Molyneux ME, Taylor TE, Wirima JJ, Borgstein A, 1989. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 71: 441–459.
- Potchen MJ et al., 2012. Acute brain MRI findings in 120 Malawian children with cerebral malaria: new insights into an ancient disease. *AJNR Am J Neuroradiol* 33: 1740–1746.
- Paul F, Roath S, Melville D, Warhurst DC, Osisanya JO, 1981. Separation of malaria-infected erythrocytes from whole blood: use of a selective high-gradient magnetic separation technique. *Lancet* 2: 70–71.
- Rasalkar DD, Paunipagar BK, Sanghvi D, Sonawane BD, Loniker P, 2011. Magnetic resonance imaging in cerebral malaria: a report of four cases. *Br J Radiol* 84: 380–385.
- Vyas S, Gupta V, Hondappanavar A, Sakhuja V, Bhardwaj N, Singh P, Khandelwal N, 2012. Magnetic resonance imaging of cerebral malaria. *J Emerg Med* 42: e117–e119.
- Maude RJ et al., 2014. Magnetic resonance imaging of the brain in adults with severe falciparum malaria. *Malar J* 13: 177.
- Seydel KB et al., 2015. Brain swelling and death in children with cerebral malaria. *N Engl J Med* 372: 1126–1137.
- Brown H, Rogerson S, Taylor T, Tembo M, Mwenechanya J, Molyneux M, Turner G, 2001. Blood-brain barrier function in cerebral malaria in Malawian children. *Am J Trop Med Hyg* 64: 207–213.
- Dorovini-Zis K, Schmidt K, Huynh H, Fu W, Whitten RO, Milner D, Kamiza S, Molyneux M, Taylor TE, 2011. The neuropathology of fatal cerebral malaria in Malawian children. *Am J Pathol* 178: 2146–2158.
- Beare NA, Harding SP, Taylor TE, Lewallen S, Molyneux ME, 2009. Perfusion abnormalities in children with cerebral malaria and malarial retinopathy. *J Infect Dis* 199: 263–271.
- Ponsford MJ, Medana IM, Prapansilp P, Hien TT, Lee SJ, Dondorp AM, Esiri MM, Day NP, White NJ, Turner GD, 2012. Sequestration and microvascular congestion are associated with coma in human cerebral malaria. *J Infect Dis* 205: 663–671.
- Brodersen P, Paulson OB, Bolwig TG, Rogon ZE, Rafaelsen OJ, Lassen NA, 1973. Cerebral hyperemia in electrically induced epileptic seizures. *Arch Neurol* 28: 334–338.
- Prohovnik I, Pavlakakis SG, Piomelli S, Bello J, Mohr JP, Hilal S, De Vivo DC, 1989. Cerebral hyperemia, stroke, and transfusion in sickle cell disease. *Neurology* 39: 344–348.
- Bartynski WS, 2008. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *AJNR Am J Neuroradiol* 29: 1036–1042.
- Haacke EM, Xu Y, Cheng YC, Reichenbach JR, 2004. Susceptibility weighted imaging (SWI). *Magn Reson Med* 52: 612–618.
- Hackett S, Hamzah J, Davis TM, St Pierre TG, 2009. Magnetic susceptibility of iron in malaria-infected red blood cells. *Biochim Biophys Acta* 1792: 93–99.
- Bosemani T, Verschuuren SI, Poretti A, Huisman TA, 2014. Pitfalls in susceptibility-weighted imaging of the pediatric brain. *J Neuroimaging* 24: 221–225.
- Beare NA, Taylor TE, Harding SP, Lewallen S, Molyneux ME, 2006. Malarial retinopathy: a newly established diagnostic sign in severe malaria. *Am J Trop Med Hyg* 75: 790–797.
- Molyneux ME, Taylor TE, Wirima JJ, Borgstein A, 1989. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 71: 441–459.
- Siemens, 2010. *MRI Protocols*. Available at: <http://www.healthcare.siemens.com/magnetic-resonance-imaging/magnetom-world/clinical-corner/protocols>. Accessed March 22, 2017.
- Potchen MJ, Kampondeni SD, Ibrahim K, Bonner J, Seydel KB, Taylor TE, Birbeck GL, 2013. NeuroInterp: a method for facilitating neuroimaging research on cerebral malaria. *Neurology* 81: 585–588.
- Hall CE, Slayter HS, 1959. The fibrinogen molecule: its size, shape, and mode of polymerization. *J Biophys Biochem Cytol* 5: 11–16.
- Moustafa RR, Baron JC, 2007. Clinical review: imaging in ischaemic stroke—implications for acute management. *Crit Care* 11: 227.
- Guimiot F, Garel C, Fallet-Bianco C, Menez F, Khung-Savatovsky S, Oury JF, Sebag G, Delezoide AL, 2008. Contribution of diffusion-weighted imaging in the evaluation of diffuse white matter ischemic lesions in fetuses: correlations with fetopathologic findings. *AJNR Am J Neuroradiol* 29: 110–115.
- Bartynski WS, 2008. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. *AJNR Am J Neuroradiol* 29: 1043–1049.
- Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng YC, 2009. Susceptibility-weighted imaging: technical aspects and clinical applications, part 1. *AJNR Am J Neuroradiol* 30: 19–30.
- Kennan RP, Machado FS, Lee SC, Desruisseaux MS, Wittner M, Tsuji M, Tanowitz HB, 2005. Reduced cerebral blood flow and N-acetyl aspartate in a murine model of cerebral malaria. *Parasitol Res* 96: 302–307.
- Lacout A, Guidoux C, Carlier CY, 2010. Posterior reversible encephalopathy syndrome in neuro-malaria. *Indian J Radiol Imaging* 20: 198–201.
- Pharmaceuticals BH, 2009. MAGNEVIST® (brand of gadopentetate dimeglumine) Injection and Pharmacy Bulk Package. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019596s043,021037s018lbl.pdf. Accessed December 20, 2017.
- Tofts PS, Kermode AG, 1991. Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts. *Magn Reson Med* 17: 357–367.