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ORIGINAL RESEARCH

Acute Brain MRI Findings in 120 Malawian Children with Cerebral Malaria: New Insights into an Ancient Disease

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BACKGROUND AND PURPOSE: There have been few neuroimaging studies of pediatric CM, a common often fatal tropical condition. We undertook a prospective study of pediatric CM to better characterize the MRI features of this syndrome, comparing findings in children meeting a stringent definition of CM with those in a control group who were infected with malaria but who were likely to have a nonmalarial cause of coma.

MATERIALS AND METHODS: Consecutive children admitted with traditionally defined CM (parasitemia, coma, and no other coma etiology evident) were eligible for this study. The presence or absence of malaria retinopathy was determined. MRI findings in children with ret+ CM (patients) were compared with those with ret− CM (controls). Two radiologists blinded to retinopathy status jointly developed a scoring procedure for image interpretation and provided independent reviews. MRI findings were compared between patients with and without retinopathy, to assess the specificity of changes for patients with very strictly defined CM.

RESULTS: Of 152 children with clinically defined CM, 120 were ret+, and 32 were ret−. Abnormalities much more common in the patients with ret+ CM were markedly increased brain volume; abnormal T2 signal intensity; and DWI abnormalities in the cortical, deep gray, and white matter structures. Focal abnormalities rarely respected arterial vascular distributions. Most of the findings in the more clinically heterogeneous ret− group were normal, and none of the abnormalities noted were more prevalent in controls.

CONCLUSIONS: Distinctive MRI findings present in patients meeting a stringent definition of CM may offer insights into disease pathogenesis and treatment.

ABBREVIATIONS: ADEM = acute disseminated encephalomyelitis; ADHD = attention deficit/hyperactivity disorder; CI = confidence interval; CM = cerebral malaria; FRFSE = fast recovery fast spin-echo; GRE = gradient recalled-echo; OR = odds ratio; ret+ = retinopathy positive; ret− = retinopathy negative

Pediatric CM affects ~3 million children annually and is responsible for one-fifth of the deaths in children <5 years of age in Sub-Saharan Africa.[1] CM is defined as asexual *Plasmodium falciparum* parasitemia and deep coma with no other coma etiology evident.[1-4] In regions with high rates of asymptomatic parasitemia and limited diagnostic capacity, the clinical diagnosis lacks specificity and may result in a >20% misclassification rate.[5] Recent research indicates that a unique malaria retinopathy can be identified acutely to confirm the diagnosis of CM with 95% sensitivity and 100% specificity in fatal cases.[6-8]

Although the exact pathophysiology is unknown, CM is associated with parasitized red blood cell sequestration in brain capillaries. Sequestration may lead to impaired perfusion and local release of inflammatory factors.[9-11] The systemic response can include hyperpyrexia, seizures, and hypoglycemia. Autopsy findings are highly variable.[5,12] The parasite produces an iron-based hemoglobin by-product, hemozoin, which often discolors the brain surface. Microhemorrhages can be seen in the cerebral white matter but not in the gray matter and in both gray and white matter in the cerebellum. In patients with prolonged coma before death, Durck granulomas (astrocyte and glial cells surrounding necrotic lesions of occluded vessels) may be evident, but objective features of herniation are seldom identified. Pediatric CM is a clinical entity distinct from the adult syndrome; thus, the neuroimaging findings may be unique to this age group.[13] It occurs primarily in resource-limited settings; thus, neuroimaging research has been limited to CT case series and MRI case reports. The largest published imaging case series was a CT study that included 14 patients.[14]

In June 2008, MRI technology became available in Malawi. We describe acute brain MRI findings in children with CM

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Frequency and characteristics of brain MRI abnormalities seen in children with ret+ versus ret− CM

Characteristics	Ret− (n = 32)	Ret+ (n = 120)	Fisher P Value	OR (95% CI)
Age (mean in months)	55.1 (27.9)	48.6 (27.6)	.23	–
Sex (% male)	40.6	54.2	–	1.72 (0.78–3.81)
Increased cerebral volume ≥4	7*	57*	.01*	3.23 (1.30–8.04)*
White matter T2 abnormalities	13*	86*	<.005*	3.7 (1.6–8.3)*
White matter DWI abnormalities	11	54	.32	1.6 (0.7–3.5)
T2 cortical abnormalities	9*	74*	.001*	4.1 (1.7–9.7)*
Cortical DWI abnormalities	5	25	.62	1.4 (0.5–4.1)
Pontine T2 changes	9	57	.07	2.3 (0.9–5.4)
T2 changes	15*	89*	.005*	3.3 (1.5–7.3)*
Basal ganglia involvement	12*	101*	<.00001*	8.9 (3.7–21.1)*
Basal ganglia DWI abnormalities	4*	48*	<.01*	4.7 (1.5–14.2)*
Thalamic involvement	10*	77*	.001*	3.9 (1.7–9.1)*
Corpus callosum T2 abnormalities	6*	59*	<.005*	4.2 (1.6–10.9)*
Corpus callosum DWI abnormalities	6*	52*	<.05*	3.3 (1.3–8.6)*
Splenium predominance	5	38	.08	2.5 (0.9–7.0)
Posterior fossa DWI abnormalities	0*	6*	.34*	Undefined
Posterior fossa signal abnormalities	7*	59*	<.01*	3.5 (1.4–8.6)*
Pre-existing abnormality	5	14	.76	0.7 (0.2–2.2)

Note:— – indicates not applicable; * statistical significance.

admitted to the pediatric research ward of Queen Elizabeth Central Hospital during the malaria seasons (January–June) of 2009 and 2010. Findings from children with ret+ CM were compared with those of the more heterogeneous group of comatose parasitemic children who met the standard clinical case definition of CM but lacked evidence of retinopathy and who were presumed to have a nonmalarial cause of coma.

Materials and Methods

Patients

Consecutive children admitted with a Blantyre Coma Scale score[15,16] of <3 who met the World Health Organization definition of CM were eligible for inclusion. Imaging was usually performed within 12 hours of admission. Children whose parents did not consent for enrollment and those who died or regained consciousness before imaging were excluded. Clinical care was provided according to standard protocols. Mechanical ventilation was not available. All subjects underwent indirect ophthalmoscopic examination by a trained clinician to determine whether malaria retinopathy was present. This work was approved by the appropriate local and US research ethics committees.

Scanning Protocols

Scans were obtained on a 0.35T Signa Ovation Excite MRI scanner (GE Healthcare, Milwaukee, Wisconsin) (On-line Figure 1). Imaging protocols in 2009 included sagittal T1 FLAIR, axial proton density, axial T2 FLAIR, axial T2 FRFSE, axial GRE, coronal T2 FRFSE, EPI-DWI b = 900, and with contrast axial T1 sequences. In 2010, these included sagittal T1 FLAIR, axial T2 FRFSE, axial T1, coronal T2 FRFSE, axial GRE, EPI-DWI b = 200, and EPI-DWI b = 900 sequences. The diffusion gradient was applied through-plane or in the superoinferior direction for the axially acquired DWI series. EPI-DWI b = 200 was added in the second year, which was the lowest b-value supported on this scanner at that time. This allowed us to calculate an ADC map, though there are some limitations without the availability of an EPI-DWI b = 0 series in this calculation. Regions of high signal intensity on the axial EPI-DWI b = 900 were interpreted as probably positive if they did not occur in anatomic areas where white matter tract orientations could lead to anisotropic effects. Regions of high signal intensity on the axial EPI-DWI b = 900 were interpreted as possibly positive if they occurred in anatomic areas where white matter tract orientation could possibly lead to an anisotropic effect.

During the first year of data collection, the T2 FLAIR sequence proved to be of limited utility, with the images exhibiting poor T2 differentiation, so this sequence was omitted from the protocol used in 2010. Also, during the first year of data collection, no focal abnormal gadolinium enhancement was seen on the postgadolinium axial T1-weighted images. Given the potential concern of continued exposure to gadolinium-based contrast agents in comatose pediatric patients without any evidence of benefit, the postgadolinium axial T1-weighted images were omitted from the protocol in 2010.

Interpretation

Two fellowship-trained radiologists, 1 in Neuroradiology (M.J.P.) and 1 in MRI (S.D.K.), read all studies. The radiologists, blinded to retinopathy status, reviewed all MRI from the research ward. After ~3 months' experience reviewing pediatric CM MRI in a mixed population of ret+ and ret− patients, they collaboratively developed a systematic scoring procedure for the patients with CM, which included graded measures of cerebral volume, periventricular white matter changes, cortical abnormalities, and T2 changes among others (Table). Cerebral volume was rated from 0 to 5 with 0 being normal. A score of grade 1–2 indicated possible increased volume. Grade 3 had obvious evidence of increase but was deemed either focal/nondiffuse or moderate in extent; patients with a score of 1–3 were not considered to have increased volume for the purpose of this analysis. A score of 4 represented significant increased volume with diffuse sulcal and cisternal effacement but without herniation, and a score of 5 required sulcal and cisternal effacement with evidence of herniation. Supratentorial cortical thickening was considered to be present under the following conditions: 1) The cortex was diffusely thickened and measured >5 mm, or 2) areas of cortical thickening were at least twice the thickness of uninvolved (ie, normal-appearing) areas. Any abnormality that was thought to be chronic in nature was categorized as a pre-existing abnormality.

The radiologists provided independent interpretations and then reviewed images together and developed a consensus interpretation

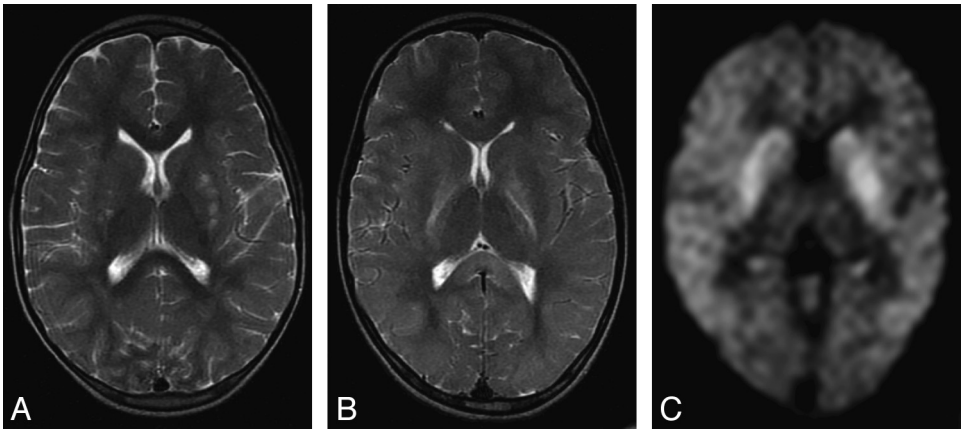

Fig 1. Basal ganglia involvement. The most common finding on initial imaging during the acute presentation was abnormal T2 signal intensity in the basal ganglia. This ranged from subtle (minimal increased T2 compared with adjacent gray matter) to marked signal-intensity changes with associated mass effect. The latter is illustrated in an axial T2 FSE image in a 6-year-old boy (*A*). Some cases showed a predilection to specific anatomic areas as seen in an axial T2 FSE image in a boy 2 years 4 months of age (*B*), in whom there was predominance in the globus pallidus with relative sparing of the other areas of the basal ganglia. *C*, Corresponding DWI image shows a common correlation in which cases of more focal basal ganglia involvement also had positive DWI findings, though sometimes in a different basal ganglia structure, in this case the putamen.

where necessary. The consensus interpretations were developed and the data base was locked before the radiologists were unblinded to retinopathy status.

Statistical Analysis

Interpretations for scans were scored and analyzed in Excel (Microsoft, Bothell, Washington). Data regarding the frequency of findings are described. Odds ratios were calculated for each of the radiologic findings in ret+ versus ret− populations, with P values of $< .05$ considered significant. No statistical corrections were made for multiple tests.

Results

Two hundred seventy children were eligible for the study. Parents declined participation for 21 children, and imaging was not possible in 94 who regained consciousness quickly and in 3 who died before imaging could be undertaken. Findings from 152 children, 120 CM ret+ cases and 32 ret− controls, are compared here. None of the 120 children with ret+ CM had normal brain MRIs.

MR Imaging Findings in Children with Ret+ versus Ret− CM

MR imaging features more common in children with ret+ CM were the following: increased cerebral volume (OR, 3.23; 95% CI, 1.30–8.04); basal ganglia involvement (OR, 8.9; 95% CI, 3.7–21.1) including DWI changes (OR, 4.7; 95% CI, 1.5–14.2); cortical abnormalities on T2 (OR, 4.1; 95% CI, 1.7–9.7); periventricular white matter changes (OR, 3.7; 95% CI, 1.6–8.3); brain stem abnormalities on T2 (OR, 3.3; 95% CI, 1.5–7.3); thalamic involvement (OR, 3.9; 95% CI, 1.7–9.1); corpus callosum changes on T2 and DWI (OR, 4.2; 95% CI, 1.6–10.9; and OR, 3.3; 95% CI, 1.3–8.6, respectively); and cerebellum (posterior fossa) changes (OR, 3.5; 95% CI, 1.4–8.6).

Abnormalities that occurred with similar frequency in the ret+ and ret− groups included white matter DWI changes, cortical DWI changes, pontine T2 changes, splenial predominance, and preexisting abnormalities.

MR Imaging Features in Children with Ret+ CM

Increased Cerebral Volume. Moderate-to-severe increased cerebral volume (grades 4 and 5) was seen in 57/120 (47.5%) with 11/120 (9.2%) of these being grade 5. These patients exhibited loss of all sulcal markings with uncal herniation and cisternal effacement. Some had unilateral hemispheric predominance with associated subfalcine herniation also identified. Although diffuse brain involvement predominated (73/92, 79.3%), there was some variability: Fourteen of 57 (24.6%) had increased volume primarily involving supratentorial regions, and 4/57 (7.0%) had predominately posterior fossa involvement.

Basal Ganglia and Thalamus. The most common finding was abnormal T2 signal intensity in the basal ganglia, present in 101/120 (84.2%) of the children with ret+ CM. This ranged from subtle, with minimal increased T2 compared with adjacent gray matter, to marked signal-intensity changes with associated mass effect (Fig 1). The normal appearance of the basal ganglia on T2 using this scanner is slightly decreased compared with adjacent gray matter. Some cases showed a predilection to specific areas (eg, predominance in the globus pallidus with relative sparing of the other areas of the basal ganglia). Positive DWI findings in the basal ganglia were present in 48/120 (40.0%) patients. The thalami showed abnormal T2 signal intensity in 77/120 (64.2%), but positive DWI findings were rare (2/120, 1.7%).

Cortical Abnormalities. Supratentorial cortical thickening and T2 signal-intensity abnormalities were present in 74/120 (61.7%) children. This generally did not follow a typical arterial vascular distribution and was confluent in some cases but distinctly multifocal in others (Fig 2). Abnormal cortical involvement included the following: 1) diffuse increased T2 signal intensity and cortical thickening, 2) predominantly posterior findings, and/or 3) frontal predominance (Fig 3).

Cortical DWI abnormalities were seen in 25/120 (20.8%) children. These often failed to correspond to a typical arterial vascular distribution. Specifically, there were no cases of watershed ischemia. Occasionally markedly asymmetric hemispheric cortical involvement was evident, confluent, and asso-

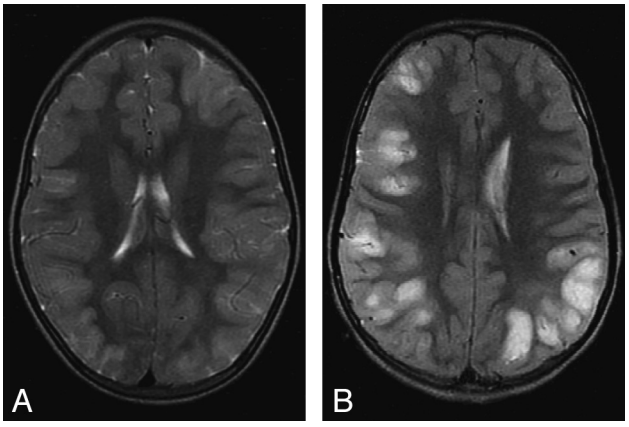

Fig 2. Cortical abnormalities. Examples of cortical abnormalities seen in ret+ CM on axial T2 FSE images. Cortical abnormalities were relatively confluent in some cases as seen in a boy 2 years 11 month of age (*A*), in whom all the visualized gray matter has increased T2 signal intensity and is diffusely thickened (>5 mm). The cortical abnormalities were distinctly multifocal in others as seen in a girl of 6 years 8 month of age (*B*), in whom there are patchy areas of involvement and areas of relative sparing. In most cases, the signal-intensity abnormalities and cortical thickening were not confined to typical arterial vascular distributions.

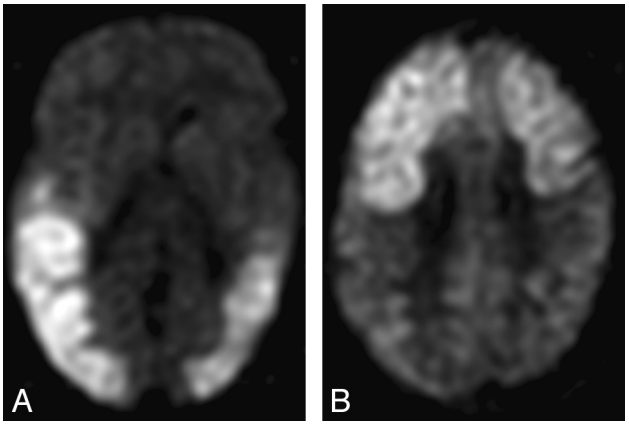

Fig 3. Patterns of cortical involvement. The patterns of affected cortical parenchyma generally fell into 1 of 3 distinct types as seen on the EPI DWI images: 1) diffuse; 2) posterior predominance, as is illustrated in a girl of 1 year 3 months of age (*A*); and 3) frontal predominance, as evident in a girl 3 years 6 months of age (*B*).

ciated with DWI abnormalities (Fig 4). As with the cortical thickening, the DWI findings did not follow a typical arterial vascular distribution.

White Matter (T2 and/or DWI). Increased T2 signal intensity in the white matter was present in 86/120 patients (71.7%) and was often associated with DWI abnormalities, which were present in 54/120 (45.0%). We identified 2 patterns of white matter involvement: 1) primarily subcortical, and 2) primarily peritrigonal (Fig 5). White matter DWI abnormalities tended to occur in the absence of cortical DWI abnormalities (Fig 6).

Corpus Callosum. T2 signal-intensity changes in the corpus callosum were present in 59/120 patients (49.2%) and often occurred in the absence of other white matter changes. Corpus callosal involvement was closely associated with corresponding positive DWI changes, seen in 52/120 (43.3%) of the total cases. Although some cases of corpus callosal abnormality had diffuse involvement, the splenium was predominantly affected in 38/52 (73.1%) cases.

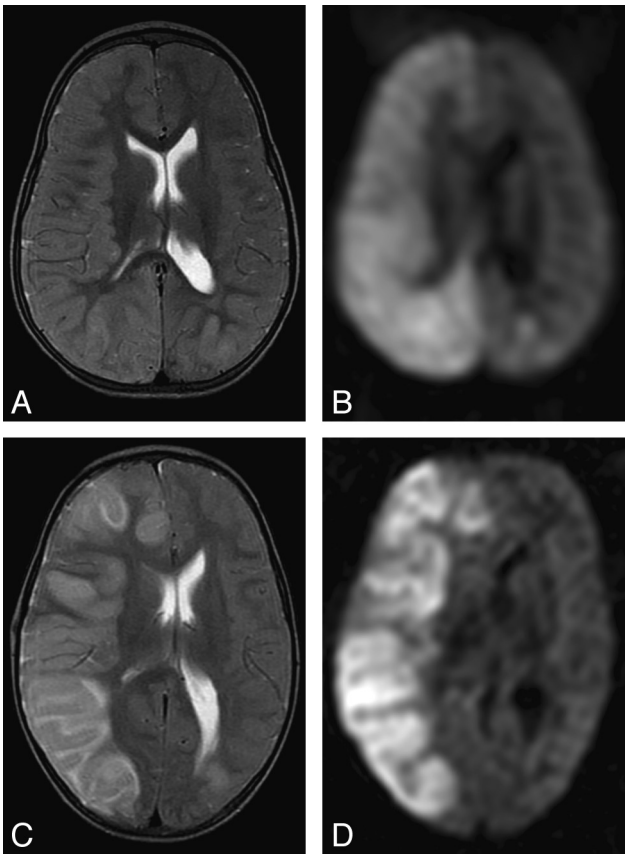

Fig 4. Asymmetric hemispheric cortical involvement. Occasionally markedly asymmetric hemispheric cortical involvement was evident. The cortical involvement tended to be confluent and associated with DWI abnormalities such as in an axial T2 FSE (*A*) and an axial EPI DWI in a girl, 2 years 7 months of age (*B*). Another example is seen in an axial T2 FSE (*C*), and an axial EPI DWI (*D*) in a boy 1 year 11 months of age. Note the associated midline shift. These patients also illustrate how children with CM frequently have constellations of findings seen in ret+ CM but, by no means are all in the same patients at the same time. For example, *A* and *B* above have subcortical white matter sparing on the T2 images, while in *C* and *D*, no subcortical white matter was involved. Also note how *A* and *B* show positive restricted diffusion in the right hemispheric white matter on the DWI images in the absence of significantly high T2 signal-intensity changes.

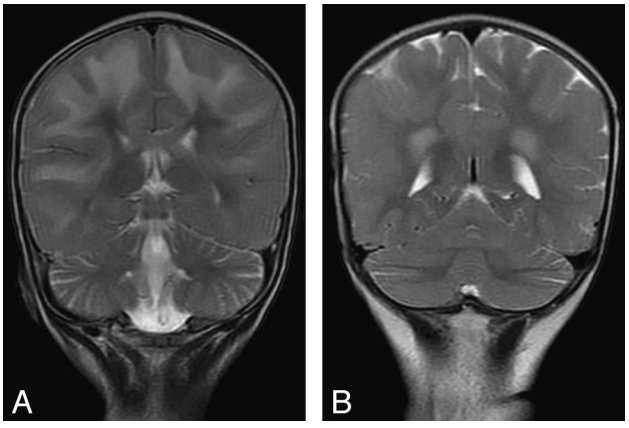

Fig 5. Distribution of white matter changes. There were 2 distinct patterns of white matter involvement: 1) primarily subcortical (*A*), a coronal T2 FSE in a boy 1 year 6 months of age; and 2) primarily peritrigonal (*B*), a coronal T2 FSE in a girl 2 years 6 months of age. These frequently coexisted, but subcortical involvement predominated.

Cerebellum. Increased T2 signal intensity was identified in the cerebellum in 59/120 (49.2%) children. This ranged from diffuse involvement with associated swelling to multifocal

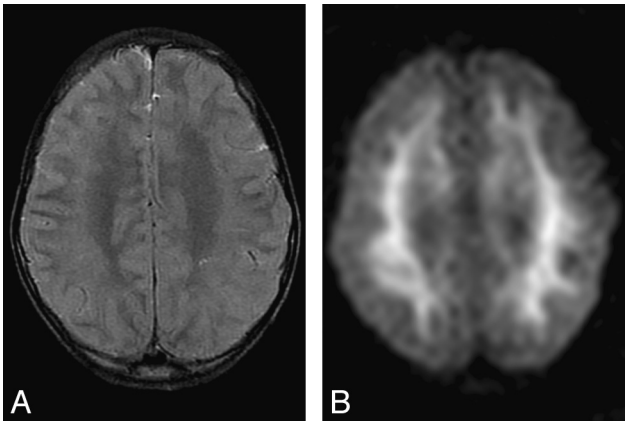

Fig 6. White matter DWI abnormalities. Subcortical white matter changes had corresponding positive DWI findings, which tended to closely follow theT2 signal-intensity abnormalities. The restricted diffusion was generally confluent and not associated with positive cortical DWI findings. We present 2 representative cases: an axial T2 FSE (*A*) and an axial EPI DWI (*B*) in a 7-year-old boy.

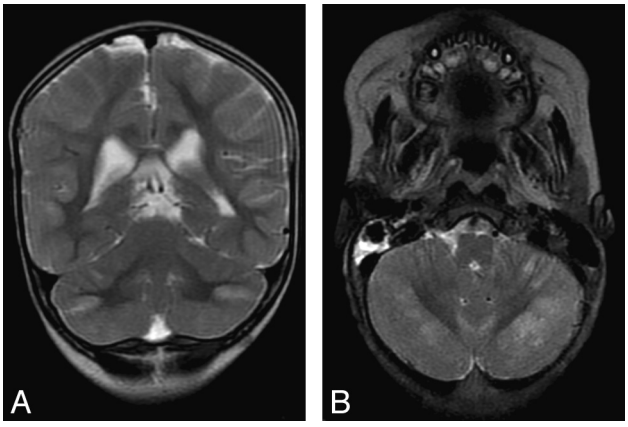

Fig 7. Posterior fossa involvement. Another common finding in ret+ CM was abnormal T2 signal intensity in the posterior fossa. This ranged from diffuse involvement of the cerebellar cortex with increased parenchymal volume to multifocal areas of cerebellar involvement, including white matter tracts, with localized mass effect as evident in a coronal T2 FSE (*A*) and an axial T2 FSE (*B*) in a boy 1 year 2 months of age. The areas and extent of involvement were unrelated to whether there was overall sparing of the posterior fossa structures compared with the presence of supratentorial disease.

areas of deep involvement with localized mass effect (Fig 7). Posterior fossa positive DWI changes were seen in 6/120 (5.0%) patients.

Treatment and Outcomes

All children received IV quinine, anticonvulsants, antibiotics, antipyretics, and blood transfusions, as clinically indicated. There was a higher mortality rate in the ret+ group (ret+, 16.7% versus ret−, 6.2%), but it was not statistically significant ($P = .17$). For survivors, time to recovery of full consciousness differed between the 2 groups with ret− children regaining consciousness sooner (ret+, 58.7 hours versus ret−, 37.7 hours; $P = .006$)

Discussion

A wide range of structural abnormalities was identified in the acute brain MRI studies of the 120 children with ret+ CM. This result is consistent with the highly variable findings identified in prior autopsy studies and underscores the complexity of this ancient disease.[5] Most of the MRI findings identified appear to be specific for retinopathy-confirmed CM. Because the ret− CM comparison group likely includes children with a range of clinical conditions and incidental parasitemia,[17,18] the specificity of the MRI findings supports the use of MRI as a means of characterizing pediatric CM.

The basal ganglia changes, evident in >80% of patients, were the most common abnormality seen. These were extensive and varied. Basal ganglia lesions or decreased volume or both are associated with behavioral disorders in children, including ADHD[19-23]; an ADHD-type behavioral problem occurs in almost 15% of CM survivors.[24] The basal ganglia lesions identified in our study are difficult to interpret because children present at different time periods after the onset of coma, owing to the vagaries of referral patterns and transportation in this setting. It is possible that these lesions follow some process of evolution during the course of the CM-related coma. Similarly, the splenial abnormalities seen in the acute phase may predict long-term sequelae associated with splenial structural abnormalities. Ongoing studies involving serial imaging and long-term follow-up will facilitate our interpretation of these findings.

Nearly 50% of children with ret+ CM had evidence of moderate-to-severe increased cerebral volume, and in nearly 10%, there was evidence of uncal and/or cerebellar herniation. These findings are consistent with brain swelling observed at autopsy[12,13] and with clinical observations suggesting raised intracranial pressure.[25,26] However, evidence of herniation has not been a hallmark of previous autopsy findings, and the underlying mechanism for the increased cerebral volume is unclear. There are several potential mechanisms for increased volume, including a localized response to inflammatory factors, parasite sequestration with venous congestion, or postischemic cytotoxic edema. Further work with serial imaging and detailed clinical correlations is ongoing.

The cortical abnormalities seen, including thickening and DWI changes, did not usually occur in an arterial vascular distribution. Whether cortical thickening represents swelling or some other process resulting in an increase in size due to the acute disease is unknown. As part of an ongoing prospective study that includes repeated imaging and imaging at discharge among survivors, we hope to gain more insight into the etiology of this thickening. Sequestration of infected erythrocytes in CM occurs in the microvasculature, and seizures are common.[16] The DWI changes may represent local ischemia due to a high metabolic demand in the setting of reduced blood flow and perhaps focal hypoglycemia, seizures, and/or hypoxia. CT studies have identified focal cortical atrophy on follow-up images from children who had focal seizures in the atrophied region during acute CM.[24] Almost 10% of child survivors of CM later develop epilepsy with localization-related seizure being the most common type. Cortical abnormalities may be a marker for an increased risk of later epilepsy in this population.

Isolated corpus callosum abnormalities have been reported with seizures, viral infections, and a number of other etiologies.[27-31] Some hypothesize that these lesions are due to intramyelinic edema, which is associated with atypical and sometimes reversible DWI abnormalities.[29] Thinning or decreased volume of the splenium has been associated with cog-

nitive impairment and behavioral abnormalities,[32] both of which occur in CM survivors.[24,33]

When we reviewed the range of imaging findings identified overall, the condition most similar to pediatric CM radiographically is ADEM.[34] Brain lesions associated with ADEM are multifocal, disseminated, and often varied in appearance. Clinically, the conditions of ADEM and CM share several features, including an abrupt onset of symptoms, early high mortality rates, and rapid recovery. However, CM and ADEM differ pathologically (personal communication, Dan Milner, MD, Harvard University, pathologist, March 7, 2011).

Pediatric CM is distinctly different from adult CM in terms of pathophysiology, autopsy findings, and clinical course.[13] Some MRI findings observed in our ret+ population (ie, periventricular white matter, thalamic, and corpus colossal involvement) have been reported in adults with CM; other adult findings (eg, cortical hemorrhage, no DWI findings) were not duplicated in our pediatric population.[35-38] This difference may be secondary to the subacute nature of the MRI studies in adults or simply because the total number of cases reported is small. No adult CM neuroimaging studies have been performed in a prospective manner.

This study has several limitations: First, the lack of availability of applying diffusion gradients on all 3 axes during axial EPI DWI imaging precludes correction of anisotropic effects. We have recently proposed and validated a 3-plane EPI DWI method of obtaining axial, coronal, and sagittal series with superoinferior, anteroposterior, and right-left $b = 900$ diffusion gradients, respectively, which will allow us to correct anisotropic effects. Second, serial MRI acquisitions, which will allow further elucidation of CM, were not included in this initial study. The lack of contrast enhancement on the postcontast studies during the initial season may well be multifactorial in nature. Whether this is due to the absence of blood-brain barrier breakdown, a limitation of the low-field magnet, or an issue with contrast delivery in this environment is uncertain. Further studies on pediatric CM on a higher field magnet aimed at addressing these questions are needed.

Conclusions

In this prospective study of brain MRI in children with acute CM (with and without malaria retinopathy), we noted that the basal ganglia were the most common area of involvement in the ret + group. Other MRI findings associated with ret+ CM included severe increased cerebral volume with herniation, focal cortical abnormalities, periventricular white matter changes, involvement of the corpus callosum, and abnormalities in the deep gray matter. The cortical changes tended to be diffuse, though a patchy non-arterial vascular distribution was also observed. The range and variability in imaging findings mirror the broad spectrum of clinical features and the variety of pathologic findings seen at autopsy. Acute focal abnormalities seen in children with CM are frequently located in brain regions in which structural abnormalities are associated with the known neuropsychiatric sequelae of CM. Unexpected findings, including frequent markedly increased cerebral volume, may offer opportunities for further clinical interventions to improve the outcomes. Ongoing studies and analyses including serial imaging during the acute coma phase will continue to provide insight into this devastating common infection.

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