Published in final edited form as:

Ann N Y Acad Sci. 2015 April ; 1342(1): 44–52. doi:10.1111/nyas.12690.

The pathogenesis of pediatric cerebral malaria: eye exams, autopsies and neuro-imaging

Terrie E. Taylor^{1,2} and Malcolm E. Molyneux^{3,4}

¹ Department of Osteopathic Medical Specialties, College of Osteopathic Medicine, Michigan State University, East Lansing MI

² Blantyre Malaria Project, University of Malawi College of Medicine, Blantyre, Malawi.

³ Liverpool School of Tropical Medicine, Liverpool, United Kingdom.

⁴ Malawi-Liverpool-Wellcome Trust Research Programme, University of Malawi College of Medicine, Blantyre, Malawi.

Abstract

Several advances in our understanding of pediatric cerebral malaria (CM) have been made over the past 25 years. Accurate clinical diagnosis is enhanced by the identification of a characteristic retinopathy, visible by direct or indirect ophthalmoscopy, the retinal changes (retinal whitening, vessel color changes, white-centered hemorrhages) being consistently associated with intracerebral sequestration of parasites in autopsy studies. Autopsies have yielded information at tissue levels in fatal CM, but new insights into critical pathogenetic processes have emerged from neuro-imaging studies which, unlike autopsy-based studies, permit serial observations over time and allow comparisons between fatal cases and survivors. Brain swelling has emerged as the major risk factor for death, and, among survivors, brain volume diminishes spontaneously over 24–48 hours. Studies of life-threatening and fatal malaria are suggesting new approaches to identifying and caring for those at highest risk; potential adjuvants should be evaluated and implemented where they are most needed.

Keywords

cerebral malaria; African children; pathogenesis; sequestration; brain swelling

Introduction

Before the mid-1970s, there had been few studies of malaria as a clinical illness. This neglect was largely due to widespread belief that, because we now understood the causal agent and its mode of transmission and had tools against both, all we needed to do was to go ahead and eradicate the disease.

Corresponding author's contact information: Terrie E. Taylor, D.O., Department of Osteopathic Medical Specialties, College of Osteopathic Medicine, Michigan State University, B309-B West Fee Hall, 909 Fee Road, East Lansing MI 4882. ttmalawi@msu.edu.

Conflicts of interest

With the failure of the Global Malaria Eradication Program, and with recognition that severe malaria carried a high case fatality rate even with the best medical care, more attention began to be paid to the individual patient and to a better understanding of disease patterns, pathogenesis and treatment. Extensive clinical studies began in patients in south-east Asia, most of whom were adults. A definition was developed that required the presence of at least one of a variety of syndromes complicating a plasmodial infection, to indicate a diagnosis of severe malaria. One of these syndromes was the characteristic encephalopathy known as cerebral malaria (CM).

With the advance of the 1980s, it was soon recognized that severe malaria had been seen as a disease of adults only because it was adult travelers who came to the attention of medical services in industrial countries. Worldwide, many more children than adults suffered from malaria infections and died from severe complications, especially in Africa. New foci of research duly sprung up, notably in The Gambia, Kenya, D.R.Congo, Ghana, Gabon, Malawi and Viet Nam.

Severe malaria in children was found to differ from the syndromes seen in adults, for example in the range of metabolic disturbances and organ involvement, speeds of evolution and resolution of disease, methods of measuring depth of coma, mortality rates, and neurological sequelae. Cerebral malaria (CM), severe anemia, hypoglycemia, metabolic acidosis and intravascular hemolysis are common forms of severe malaria in children, and may occur singly or in any combination. Life-threatening organ complications common in adults – renal, pulmonary and coagulation failure in particular – have been less commonly reported in children. Acute kidney injury, defined as an elevated blood urea nitrogen, was significantly associated with mortality in a retrospective analysis of a large pediatric clinical trial, suggesting that it would benefit from careful prospective investigation^{1,2}, but persisting oliguric or anuric renal failure is rarely encountered as a complication of malaria in children. This review will focus on the evolution of our understanding of the pathogenesis of *cerebral malaria* in African children, drawing on data generated by research activities, particularly in Malawi.

Clinical characterization of CM in children

Case definition

Before 1980, most clinicians regarded any manifestation of cerebral dysfunction in an individual with malaria infection as cerebral malaria, but a more rigorous definition was developed during studies of Thai adults³: unrousable coma (non-localizing response to a noxious stimulus) persisting for more than six hours after a convulsion, exclusion of other encephalopathies (hypoglycemia, meningoencephalitis, intoxications, metabolic disturbances, eclampsia, head injuries, cerebrovascular accidents), and confirmation of *P. falciparum* infection (asexual forms in circulating blood or bone marrow during life or in brain tissue after death).

Early efforts in the pediatric arena focused on developing a reproducible measure of depth of coma, and the most enduring of these is the Blantyre Coma Score in which the response to painful stimuli (pressure on the nail bed, sternum or supraorbital ridge) is graded on the

basis of the physical response (none/extension, withdrawal, localizing) and on the verbal response (none, abnormal cry, normal cry/verbal response)⁴. In addition, the patient's ability (no/yes) to fix her gaze and to follow a moving object is determined. In children with CM, a Blantyre score of 2 or less corresponds to being unable to localize a painful or noxious stimulus and is associated with mortality rates of 15-40%^{4, 5}, children with scores of 3 or more on this scale have a better prognosis.

Metabolic abnormalities

The importance of pre-treatment hypoglycemia was noted in the early studies; a small proportion of unconscious, malaria-infected children with low blood glucose levels improved after the administration of concentrated dextrose⁶, but most did not, and in that subset – fulfilling the definition of CM – outcomes were worse⁷. The worst outcomes of all were seen in children who experienced recurrent bouts of hypoglycemia, even when blood glucose concentrations were maintained in the normal range. These studies excluded starvation and hyperinsulinemia as etiologies and suggested that impaired hepatic gluconeogenesis and parasite glucose consumption were important in the pathogenesis of hypoglycemia.

Metabolic acidosis was identified as an important feature of severe malaria in children, with or without concomitant neurological abnormalities^{8, 9}. Initially described on the basis of clinical observations of Kussmaul (deep) respirations in the absence of clinical findings of pneumonia, a plasma bicarbonate concentration < 15 mmol/L was found to be associated with worse outcomes in children presenting to hospital with malaria-associated fevers. The advent of point-of-care lactate monitors facilitated the study of this phenomenon, although acidosis and hyperlactatemia may not always reflect the same underlying perturbations¹⁰. Hyperlactatemia is consistently a poor prognostic feature in pediatric patients with severe malaria, as it is in other severe infections in children, but its etiology is not entirely clear. Hypovolemia was an early consideration, but data from detailed studies of intravascular volume in severe pediatric malaria were conflicting^{11, 12}. A large clinical trial of intravascular volume replacement in African children with a variety of infections, including malaria, demonstrated that intravenous boluses of crystalloids and colloids were not helpful¹³, even in children with acidosis/hyperlactatemia and shock, supporting previous concerns based on volume adequacy in such groups¹⁴.

Hematologic abnormalities

Anemia is frequently a concomitant complication in patients with cerebral malaria; in one study from Blantyre, 36% of CM patients also had severe malarial anemia (SMA)([Hb]<5g/dl). The case fatality rate in the group with both CM and SMA (20.4%) was significantly higher than in the group with CM only (15.7%). Platelet counts are low in all clinical malaria syndromes, but among children with CM the degree of thrombocytopenia does not appear to predict outcome¹⁵.

Co-infections

Bacteremia rates in children with severe malaria range from 4.6% in Blantyre, Malawi¹⁶ to 7.8% in Kilifi, Kenya¹⁷. Concomitant bacterial infections, most commonly with non-

typhoidal *Salmonellae*, were a risk factor for death in Kenya, but not in Malawi. The impact of HIV co-infection on the course of cerebral malaria was associated with higher parasite burden, more complications and a higher case fatality rate in a study in Maputo, Mozambique¹⁸. In Malawi, a similar study failed to demonstrate those associations¹⁶, possibly because of the inclusion in Malawi of retinopathy as a criterion for the diagnosis of CM.

Eye findings

In 1993, previous descriptions of retinal hemorrhages in cerebral malaria patients were extended by the recognition of a striking constellation of ocular fundoscopic findings in Malawian children with CM: macular and extra-macular retinal whitening, vessel color changes and the white-centered appearance of most retinal hemorrhages¹⁹ (Fig. 1). All three features can also be seen in fully conscious children with severe malarial anemia, but the prevalence of retinal changes is low in this group²⁰. Autopsy-based studies have shown that the number of cerebral micro-hemorrhages correlates with that of white-centered ocular hemorrhages²¹, and that ocular vessel color changes are associated with the presence of sequestered parasitized red cells within the vessels²². The mechanism underlying retinal whitening was revealed by fluorescein angiography, which showed blocked capillaries (non-perfusion) coinciding exactly with areas of whitening seen by ophthalmoscopy²³. Malarial retinopathy was not a consistent feature in children who satisfied the standard clinical case definition of CM, but at least one of these findings was present in ~2/3 of the CM patients, and the more extensive the changes, the worse the outcome²⁴.

The moments before death

Few clinical settings in sub-Saharan Africa are equipped with ventilators, so deaths ensue shortly after the fatal insult. Careful clinical studies in Kilifi documented a rostro-caudal progression of neurological signs in 9 of 12 fatal cases; in each of these children, death resulted from a respiratory arrest with adequate cardiac output, despite hand ventilation for up to 48 hours²⁵. Subsequently, computed tomography (CAT scans) showed evidence of increased brain volume in six of 14 CM survivors; the other heterogeneous findings were consistent with decreased cerebral perfusion pressure²⁶. When direct measures of intracranial pressure were made, again in Kilifi, four of 23 children had severe intracranial hypertension, and of these, two died of herniation²⁷. These clinical observations were consistent with raised intracranial pressure being a mechanism of death in a subset of patients who met the standard clinical case definition of cerebral malaria.

Clinicopathological correlates

Early 20th century autopsy studies were of adults taking part in military campaigns in malaria-endemic areas^{28, 29}, while studies in children were largely limited to case reports. A study of fatal pediatric CM was commenced in Malawi in 1996, comparing children meeting the standard clinical case definition with controls (non-malarial coma, severe malarial anemia without coma). In the event of a death, permission was sought from the families to carry out a complete autopsy. Over the course of the study, 2,291 patients were admitted,

404 died, 335 families were approached for permission, and 103 families agreed to allow an autopsy to be carried out³⁰.

Sequestration

Among 31 cases of clinically defined cerebral malaria, 3 different patterns of sequestration in the cerebral microvasculature were described : CM1 refers to the presence of sequestered parasites in >23% of cerebral capillaries in cross-section, without further changes; CM2 is sequestration at the same or higher level of intensity plus intra- and peri-vascular evidence of hemorrhage, thrombi, and extra-erythrocytic hemozoin (Fig. 2); and CM3 describes patients in whom there was very little evidence of any sequestration.^{31, 32} Overall, 21% of patients had the CM1 pattern, 63% had CM2, and 16% had CM3³⁰.

At autopsy, a non-malarial cause of death was identified in all patients with the CM3 histologic pattern. The causes were varied (ruptured arterio-venous malformation with subdural hemorrhage, massive hepatic necrosis, pneumonia), but all occurred in children with coma, *P. falciparum* parasitemia, and no other obvious cause of coma³¹. Without the autopsy, the actual causes of death would have remained unknown. This misclassification represents a source of imprecision in studies of CM, and may misdirect the clinical management of individual patients.

Clinical features associated with cerebral sequestration

Among patients meeting the standard clinical case definition of cerebral malaria, only three clinical features reliably distinguished those with CM1 and CM2 from those with CM3: platelet count¹⁵, plasma concentrations of histidine-rich protein 2 (HRP2)³³ and the presence of at least one sign of malarial retinopathy³¹. Of these, ocular funduscopy is the most readily employed at the bedside. Including findings from direct and indirect ophthalmoscopy improves the standard clinical case definition of CM significantly. The enhanced specificity increases the efficiency of clinical studies of pediatric cerebral malaria; the absence of malarial retinopathy in comatose, parasitemic children should prompt a search for other etiologies of coma³⁴

Neuropathology summary

A detailed neuropathological study of this same group of patients revealed increased brain weight (for age) in a majority of cases in all categories (i.e., cases of clinically defined CM and controls)³⁵. There was axonal and myelin damage associated with ring hemorrhages and thrombosis in patients with CM2, and with sequestration alone in patients with CM1 and CM2. Blood-brain barrier disruption was seen in association with ring hemorrhages, and also with thrombosis and sequestration. Intravascular monocytes accumulated in vessels containing sequestered parasitized red cells in CM2 cases, but were not present in the adjacent brain parenchyma. No convincing alternative or additional causes of death could be identified on the basis of gross or histologic pathology in patients with CM1 or CM2 forms of sequestration.

Insights from neuroimaging

Two inherent limitations of autopsy-based studies are that findings emanate from a single point in time (the moment of death), precluding the identification of processes unfolding over time, and that data are only available from the patients who die, which prevents any comparisons with survivors. Both of these limitations can be overcome with neuroimaging³⁶. Ten Thai adults³⁷, fourteen Kenyan children,²⁶ nearly 150 Indian adults,^{38, 39} all meeting the standard clinical case definition of CM, and 56 Malawian children with retinopathy-positive CM were imaged by CT.⁴⁰ Brain swelling was the most common abnormality and was only associated with a poor clinical outcome in the Malawi study; the other clinical findings were quite heterogeneous³⁶.

The capacity for magnetic resonance imaging arrived in Malawi in 2008, the result of a generous donation from General Electric Healthcare. Initial efforts focused on identifying findings characteristic of children with retinopathy-positive CM;⁴¹ more recently, 168 children with retinopathy-positive CM were included in a study designed to identify clinical, MRI and EEG features associated with a fatal outcome. In the multivariate analysis, three MRI features (increased brain volume per radiologist assessment, decreased width of pre-pontine CSF, and a pattern of posterior cerebral predominance) and one EEG finding (decreased voltage) were associated with a poor outcome (Seydel, *et al*, submitted). Two of the three MRI findings are clearly associated with brain swelling, and the third, along with the EEG finding, reflect impaired cerebral perfusion. In the Malawi series, the case fatality rate in children *without* increased brain volume was only 4%. Overall, 40% of children with retinopathy-positive CM have MRI evidence of increased brain volume, and in this group the case fatality is 37%. Among patients who had serial MRIs, brain volume continued to increase in fatal cases (Fig. 3), and spontaneously decreased in survivors.

The combination of the MRI findings (with brain swelling almost invariably seen in fatal pediatric CM, but uncommon in non-fatal CM) and the bedside observations (deaths following sudden respiratory arrests) suggests that raised intracranial pressure (ICP) and its complications (herniation, impaired cerebral blood flow) are contributing to the fatal outcomes.

Why were the classic macroscopic findings of this mode of death (cerebellar tonsillar grooving, Duret hemorrhages) not apparent in the Malawi autopsy series? Possible explanations include the rapidity with which death ensued after the neurological insult (ventilatory support was not an option) and with which the autopsies commenced (all were carried out within 12 hours of death), and the necessity of removing the skull cap (in effect, a decompressive craniotomy) in order to access the brain during the post mortem. The natural history of the brain swelling (per MRI) suggests that increased ICP is transient in survivors; interventions that diminish brain volume enough to prevent herniation or that provide ventilatory support during the high-risk period might be sufficient to decrease the case fatality rate in pediatric CM.

Next steps

Having now honed in on the group of retinopathy-positive CM patients at highest risk of dying (Figure 4), identifying adjunctive therapy targeting increased brain volume becomes a high priority. A number of clinical trials targeting various putative mechanisms (cerebral edema^{3, 42}, sequestration⁴³, inflammation⁴⁴, decreased red cell deformability^{45, 46}, coagulation abnormalities⁴⁷ vasogenic edema^{39, 48} have been carried out, but none improved clinical outcomes. There are several possible explanations for the trial failures: the trials were underpowered (there were probably high rates of misclassification, especially because these studies were conducted prior to the appreciation of the malarial retinopathy criterion³¹; the putative mechanism was not critical to the pathogenesis of fatal malaria; the mechanism was relevant, but the intervention was timed ineffectively; and/or the primary outcome was death, and only a very large study can detect a small but statistically significant decrease in case fatality⁴⁹.

One approach is to use new information and new approaches to identify the underlying etiology, and target treatment accordingly.

Potential etiologies of increased brain volume

Increased brain volume can result from a number of different molecular, cellular, structural or functional changes in the blood-brain barrier, the microcirculation, or various autoregulatory systems⁵⁰. Because intracranial space is limited and fixed (once the fontanelles close), any additional increase in intracranial volume can cause an increase in ICP, which will, in turn, aggravate and accelerate the original insults and injuries. There are several potential mechanisms for the severe increase in brain volume observed in CM patients, including

- the diffuse mass of sequestered parasites causing venous congestion
- vasogenic edema associated with blood-brain barrier disruption
- increased cerebral blood flow volume as a result of anemia, seizures and fever
- post-ischemic cytotoxic edema

The clinical phenotype of increased brain volume is useful in evaluating proposed pathogenetic mechanisms in severe malaria. For instance, recent findings regarding the molecular mechanisms underlying the sequestration of parasitized red cells in the cerebral microvessels suggest that certain parasite variants (those expressing DC8 and DC13 *var* genes) are more commonly seen in children with severe malaria⁵¹. These parasites bind well to an endothelial cell surface protein, endothelial cell protein C receptor (EPCR)⁵², and the interaction may block access to the protein⁵³. This could impair the usual anti-inflammatory effects of EPCR activation, creating a more pro-inflammatory state in children with severe malaria, and if this also results in increased brain volume, this mechanism would be worth targeting.

Clinical trials of interventions

Mechanism-driven: Depending on the relative contributions of each of these the putative mechanisms of increased brain volume, potential therapeutic interventions could include one or more of the following: elevating the head of the bed (to facilitate venous drainage), high dose corticosteroids (for vasogenic edema), osmotic interventions (mannitol or hypertonic saline) to address cytotoxic edema, and aggressive management of fevers, anemia and seizures to diminish the cerebral blood flow volume. Using malarial retinopathy to identify patients with clinically defined CM who are likely to have cerebral sequestration, and honing in on the subset at highest risk of death, those with increased brain volume, would increase the efficiency of an interventional clinical trial (Figure 4). The natural history of increased brain volume suggests that complete resolution would not be required of an intervention; the goal would be to prevent herniation.

Process driven: Given the rapid resolution of increased brain volume (per MRI) in Malawian survivors of CM and the lack of multi-organ system involvement in pediatric malaria, the potential of short-term ventilatory support as an intervention is appealing. Robust ventilators capable of delivering oxygen from cost-effective oxygen concentrators (rather than expensive cylinders of compressed gas) have been developed and deployed in developing country settings^{54, 55}. With this approach, the goals would be to maintain ventilation in periods of respiratory inadequacy, exhaustion or arrest, incorporating modest hyperventilation to reduce brain volume via vasoconstriction, during the period of highest risk, and to remove the ventilatory support once the brain volume is no longer dangerously high.

Conclusion

Measures to combat malaria – including drugs, insecticides, bednets, environmental control and vaccines – now allow guarded optimism about the elimination of the infection country by country and its eventual global eradication. But even the most confident predictions recognize that malaria will persist – if, hopefully, in fewer places – for several decades to come, and that resistance to drugs, insecticides and vaccines, together with waning immunity and climate changes, may threaten progress. Cerebral malaria, along with other complications of *P falciparum* infection, will continue to claim victims.

Studies of life-threatening and fatal malaria are suggesting new approaches to identifying and caring for those at greatest risk, and it is urgent that these new possibilities be tested and applied where they are most needed.

References

1. Dondorp A, Nosten F, Stepniewska K, et al. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet*. 2005; 366:717–725. [PubMed: 16125588]
2. von Seidlein, L.; Olaosebikan, R.; Hendriksen, IC., et al. *Clin Infect Dis*. Vol. 54. United States: 2012. Predicting the clinical outcome of severe falciparum malaria in african children: findings from a large randomized trial.; p. 1080-1090.

3. Warrell DA, Looareesuwan S, Warrell MJ, et al. Dexamethasone proves deleterious in cerebral malaria. A double-blind trial in 100 comatose patients. *N Engl J Med.* 1982; 306:313–319. [PubMed: 7033788]
4. Molyneux ME, Taylor TE, Wirima JJ, et al. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med.* 1989; 71:441–459. [PubMed: 2690177]
5. Newton CR, Chokwe T, Schellenberg JA, et al. Coma scales for children with severe falciparum malaria. *Trans R Soc Trop Med Hyg.* 1997; 91:161–165. [PubMed: 9196757]
6. White NJ, Warrell DA, Chanthavanich P, et al. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med.* 1983; 309:61–66. [PubMed: 6343877]
7. Taylor TE, Molyneux ME, Wirima JJ, et al. Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria. *N Engl J Med.* 1988; 319:1040–1047. [PubMed: 3050516]
8. Taylor TE, Borgstein A, Molyneux ME. Acid-base status in paediatric *Plasmodium falciparum* malaria. *Q J Med.* 1993; 86:99–109. [PubMed: 8464997]
9. Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. *N Engl J Med.* 1995; 332:1399–1404. [PubMed: 7723795]
10. Newton CR, Krishna S. Severe falciparum malaria in children: current understanding of pathophysiology and supportive treatment. *Pharmacol Ther.* 1998; 79:1–53. [PubMed: 9719344]
11. Jarvis JN, Planche T, Bicanic T, et al. Lactic acidosis in Gabonese children with severe malaria is unrelated to dehydration. *Clin Infect Dis.* 2006; 42:1719–1725. [PubMed: 16705578]
12. Maitland K, Pamba A, English M, et al. Pre-transfusion management of children with severe malarial anaemia: a randomised controlled trial of intravascular volume expansion. *Br J Haematol.* 2005; 128:393–400. [PubMed: 15667544]
13. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med.* 2011; 364:2483–2495. [PubMed: 21615299]
14. Planche T, Onanga M, Schwenk A, et al. Assessment of volume depletion in children with malaria. *PLoS medicine.* 2004; 1:e18. [PubMed: 15526044]
15. Chimalizeni Y, Kawaza K, Taylor T, et al. The platelet count in cerebral malaria, is it useful to the clinician? *Am J Trop Med Hyg.* 2010; 83:48–50. [PubMed: 20595476]
16. Bronzan RN, Taylor TE, Mwenechanya J, et al. Bacteremia in Malawian children with severe malaria: prevalence, etiology, HIV coinfection, and outcome. *J Infect Dis.* 2007; 195:895–904. [PubMed: 17299721]
17. Berkley J, Mwarumba S, Bramham K, et al. Bacteraemia complicating severe malaria in children. *Trans R Soc Trop Med Hyg.* 1999; 93:283–286. [PubMed: 10492760]
18. Hendriksen IC, Ferro J, Montoya P, et al. Diagnosis, clinical presentation, and in-hospital mortality of severe malaria in HIV-coinfected children and adults in Mozambique. *Clin Infect Dis.* 2012; 55:1144–1153. [PubMed: 22752514]
19. Lewallen S, Taylor TE, Molyneux ME, et al. Ocular fundus findings in Malawian children with cerebral malaria. *Ophthalmology.* 1993; 100:857–861. [PubMed: 8510897]
20. Beare NA, Southern C, Chalira C, et al. Prognostic significance and course of retinopathy in children with severe malaria. *Arch Ophthalmol.* 2004; 122:1141–1147. [PubMed: 15302654]
21. White VA, Lewallen S, Beare N, et al. Correlation of retinal haemorrhages with brain haemorrhages in children dying of cerebral malaria in Malawi. *Trans R Soc Trop Med Hyg.* 2001; 95:618–621. [PubMed: 11816433]
22. Lewallen S, White VA, Whitten RO, et al. Clinical-histopathological correlation of the abnormal retinal vessels in cerebral malaria. *Arch Ophthalmol.* 2000; 118:924–928. [PubMed: 10900105]
23. Beare NA, Harding SP, Taylor TE, et al. Perfusion abnormalities in children with cerebral malaria and malarial retinopathy. *J Infect Dis.* 2009; 199:263–271. [PubMed: 18999956]
24. Beare NA, Lewallen S, Taylor TE, et al. Redefining cerebral malaria by including malaria retinopathy. *Future Microbiol.* 2011; 6:349–355. [PubMed: 21449844]
25. Newton CR, Kirkham FJ, Winstanley PA, et al. Intracranial pressure in African children with cerebral malaria. *Lancet.* 1991; 337:573–576. [PubMed: 1671941]

26. Newton CR, Peshu N, Kendall B, et al. Brain swelling and ischaemia in Kenyans with cerebral malaria. *Arch Dis Child*. 1994; 70:281–287. [PubMed: 8185359]
27. Newton CR, Crawley J, Sowumni A, et al. Intracranial hypertension in Africans with cerebral malaria. *Arch Dis Child*. 1997; 76:219–226. [PubMed: 9135262]
28. Spitz S. The pathology of acute falciparum malaria. *Mil Surg*. 1946; 99:555–572. [PubMed: 20276800]
29. Halder K, Murphy SC, Milner DA, et al. Malaria: mechanisms of erythrocytic infection and pathological correlates of severe disease. *Annual review of pathology*. 2007; 2:217–249.
30. Milner DA, Whitten RO, Kamiza S, et al. The systemic pathology of cerebral malaria in African children. *Front Cell Infect Microbiol*. 2014; 4:104. [PubMed: 25191643]
31. Taylor T, Fu W, Carr R, et al. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. *Nat Med*. 2004; 10:143–145. [PubMed: 14745442]
32. Milner DA, Valim C, Carr RA, et al. A histological method for quantifying *Plasmodium falciparum* in the brain in fatal paediatric cerebral malaria. *Malar J*. 2013; 12:191. [PubMed: 23758807]
33. Seydel KB, Fox LL, Glover SJ, et al. Plasma concentrations of parasite histidine-rich protein 2 distinguish between retinopathy-positive and retinopathy-negative cerebral malaria in Malawian children. *J Infect Dis*. 2012; 206:309–318. [PubMed: 22634877]
34. Postels DG, Birbeck GL. Children with retinopathy-negative cerebral malaria: a pathophysiologic puzzle. *The Pediatric infectious disease journal*. 2011; 30:953–956. [PubMed: 21694660]
35. Dorovini-Zis K, Schmidt K, Huynh H, et al. The neuropathology of fatal cerebral malaria in malawian children. *Am J Pathol*. 2011; 178:2146–2158. [PubMed: 21514429]
36. Mohanty S, Taylor TE, Kampondeni S, et al. Magnetic resonance imaging during life: the key to unlock cerebral malaria pathogenesis? *Malar J*. 2014; 13:276. [PubMed: 25038815]
37. Looareesuwan S, Warrell DA, White NJ, et al. Do patients with cerebral malaria have cerebral oedema? A computed tomography study. *Lancet*. 1983; 1:434–437. [PubMed: 6131165]
38. Patankar TF, Karnad DR, Shetty PG, et al. Adult cerebral malaria: prognostic importance of imaging findings and correlation with postmortem findings. *Radiology*. 2002; 224:811–816. [PubMed: 12202719]
39. Mohanty S, Mishra SK, Patnaik R, et al. Brain swelling and mannitol therapy in adult cerebral malaria: a randomized trial. *Clin Infect Dis*. 2011; 53:349–355. [PubMed: 21810747]
40. Potchen MJ, Birbeck GL, Demarco JK, et al. Neuroimaging findings in children with retinopathy-confirmed cerebral malaria. *Eur J Radiol*. 2010; 74:262–268. [PubMed: 19345538]
41. Potchen MJ, Kampondeni SD, Seydel KB, et al. Acute brain MRI findings in 120 Malawian children with cerebral malaria: new insights into an ancient disease. *AJNR Am J Neuroradiol*. 2012; 33:1740–1746. [PubMed: 22517285]
42. Hoffman SL, Rustama D, Punjabi NH, et al. High-dose dexamethasone in quinine-treated patients with cerebral malaria: a double-blind, placebo-controlled trial. *J Infect Dis*. 1988; 158:325–331. [PubMed: 3042874]
43. Taylor TE, Molyneux ME, Wirima JJ, et al. Intravenous immunoglobulin in the treatment of paediatric cerebral malaria. *Clinical and experimental immunology*. 1992; 90:357–362. [PubMed: 1458672]
44. van Hensbroek MB, Palmer A, Onyiorah E, et al. The effect of a monoclonal antibody to tumor necrosis factor on survival from childhood cerebral malaria. *J Infect Dis*. 1996; 174:1091–1097. [PubMed: 8896514]
45. Di Perri G, Di Perri IG, Monteiro GB, et al. Pentoxifylline as a supportive agent in the treatment of cerebral malaria in children. *J Infect Dis*. 1995; 171:1317–1322. [PubMed: 7751709]
46. Lell B, Kohler C, Wamola B, et al. Pentoxifylline as an adjunct therapy in children with cerebral malaria. *Malar J*. 2010; 9:368. [PubMed: 21176151]
47. Hemmer CJ, Kern P, Holst FG, et al. Neither heparin nor acetylsalicylic acid influence the clinical course in human *Plasmodium falciparum* malaria: a prospective randomized study. *Am J Trop Med Hyg*. 1991; 45:608–612. [PubMed: 1951871]

48. Namutangula B, Ndeezi G, Byarugaba JS, et al. Mannitol as adjunct therapy for childhood cerebral malaria in Uganda: a randomized clinical trial. *Malar J.* 2007; 6:138. [PubMed: 17958887]
49. Enwere G. A review of the quality of randomized clinical trials of adjunctive therapy for the treatment of cerebral malaria. *Trop Med Int Health.* 2005; 10:1171–1175. [PubMed: 16262742]
50. Pappius HM. Spaces in brain tissue in vitro and in vivo. *Prog Brain Res.* 1968; 29:455–464. [PubMed: 5735121]
51. Lavstsen T, Turner L, Saguti F, et al. Plasmodium falciparum erythrocyte membrane protein 1 domain cassettes 8 and 13 are associated with severe malaria in children. *Proc Natl Acad Sci U S A.* 2012; 109:1791–1800.
52. Turner L, Lavstsen T, Berger SS, et al. Severe malaria is associated with parasite binding to endothelial protein C receptor. *Nature.* 2013; 498:502–505. [PubMed: 23739325]
53. Moxon CA, Wassmer SC, Milner DA, et al. Loss of endothelial protein C receptors links coagulation and inflammation to parasite sequestration in cerebral malaria in African children. *Blood.* 2013; 122:842–851. [PubMed: 23741007]
54. Riviello ED, Letchford S, Achieng L, et al. Critical care in resource-poor settings: lessons learned and future directions. *Crit Care Med.* 2011; 39:860–867. [PubMed: 21297458]
55. Baker T. Critical care in low-income countries. *Trop Med Int Health.* 2009; 14:143–148. [PubMed: 19207174]

Figure 1. Features of malarial retinopathy. Fundus photographs from pediatric patients in Malawi illustrate the 3 components of malarial retinopathy. (A) White centered hemorrhages. (B) Vessel color changes are evident in the branching veins in the center of this image. (C) Perimacular whitening (shown within the circle) is distinct from the reflections created by the fundus camera

Figure 2.

Postmortem findings (CM2). The gross and microscopic findings associated with the histologic subtype CM2 are shown here. (A) A slate gray appearance of the surface of the brain at autopsy. The flattened gyri and narrowed sulci are consistent with the MRI findings of increased brain volume in fatal pediatric CM. (B and C) A coronal section of the brain at the time of autopsy shows the characteristic distribution of hemorrhages in the white matter of the cerebral cortex. (D) A post-capillary venule with parasitized red cells surrounding a central column of unparasitized red cells. This appearance is also seen in CM1 patients. (E and F). Low and higher power images of ring hemorrhages in cortical white matter. Thrombi are present in the center of each vessel; extravasated erythrocytes are unparasitized.

Figure 3. MRI features in a fatal case of pediatric CM. These T2 images from the 0.35T MRI in Malawi illustrate the natural history of increasing brain volume in children with fatal CM. (A) MRI from a recovered patient, showing rounded gyri, in black, cerebrospinal fluid in the sulci and surrounding the brainstem. (B and C). These two studies were carried out on the same patient, 24 h apart. Flattened gyri and narrowed sulci are evident in both, and encroachment of the cerebellar tonsils on the brainstem, indicating herniation, is seen in C, 4 hours prior to death.

Figure 4.

Identifying high-risk pediatric malaria patients. (A and B) In a group of children in a malaria-endemic region of sub-Saharan Africa, a proportion will be uninfected (A, pink), while others will have asymptomatic parasitemia (B, light purple). Some of these children will develop uncomplicated malaria (B, darker purple) and a few will progress to severe and complicated malaria (B, black). (C) Children meeting the standard clinical case definition of cerebral malaria are shown in (black). (D) Adding ocular fundusoscopic findings enhances the specificity of the diagnosis: retinopathy-negative patients are shown in blue, and the retinopathy-positive patients are yellow and red. (E) Only patients with retinopathy-positive CM, and among that group, the children at highest risk of a fatal outcome are those with brain swelling, shown in red in panels D, E, and F. Fatal cases are indicated with a cross.