

REVIEW ARTICLE

Cerebral Malaria: Mechanisms of Brain Injury and Strategies for Improved Neurocognitive Outcome

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ABSTRACT: Cerebral malaria is the most severe neurological complication of infection with *Plasmodium falciparum*. With >575,000 cases annually, children in sub-Saharan Africa are the most affected. Surviving patients have an increased risk of neurological and cognitive deficits, behavioral difficulties, and epilepsy making cerebral malaria a leading cause of childhood neurodisability in the region. The pathogenesis of neurocognitive sequelae is poorly understood: coma develops through multiple mechanisms and there may be several mechanisms of brain injury. It is unclear how an intravascular parasite causes such brain injury. Understanding these mechanisms is important to develop appropriate neuroprotective interventions. This article examines possible mechanisms of brain injury in cerebral malaria, relating this to the pathogenesis of the disease, and explores prospects for improved neurocognitive outcome. (*Pediatr Res* 68: 267–274, 2010)

Cerebral malaria is the most severe neurological complication of infection with *Plasmodium falciparum* malaria. It is a clinical syndrome characterized by coma and asexual forms of the parasite on peripheral blood smears. Mortality is high and some surviving patients sustain brain injury that manifest as long-term neurocognitive impairments. In this article, we review studies that have provided current understanding of the pathogenesis of brain injury and explore prospects for neuroprotection and improved outcome.

Epidemiology

Falciparum malaria is a leading cause of ill health, neurodisability, and death in tropical countries. Although 40% of the world's population is at risk, most transmission occurs in sub-Saharan Africa, where children younger than 5 y are the most affected and the incidence of disease declines in older children with increasing immunity. In South-East Asia, malaria occurs more commonly in adults but the clinical features are different (1).

Every year, there are >500 million clinical cases. One percent of symptomatic infections may become complicated and develop into severe malaria. Severe malaria may manifest as anemia, hypoglycemia, metabolic acidosis, repeated seizures, coma, or multiple organ failure and is estimated to cause >1 million deaths annually (1). Cerebral malaria is the most severe neurological manifestation of severe malaria. With an incidence of 1,120/100,000/y in the endemic areas of Africa, children in this region bear the brunt. Peak incidence is in preschool children and at a minimum, 575,000 children in Africa develop cerebral malaria annually (2). However, recent reports suggest that the incidence of severe malaria is on the decline (3,4).

Clinical Features

The clinical features of cerebral malaria have been reviewed extensively (5,6). In this article, we highlight some of the main features.

The World Health Organization defines cerebral malaria as a clinical syndrome characterized by coma at least 1 h after termination of a seizure or correction of hypoglycemia, asexual forms of *Plasmodium falciparum* parasites on peripheral blood smears, and no other cause to explain the coma (7). In practice, this definition is nonspecific. Patients in whom coma is caused by other encephalopathies (e.g. viral encephalitis, poisoning, and metabolic disease) or previously unrecognized neurological abnormalities but have incidental parasitemia (a common phenomenon in malaria endemic areas) may be included. Thus, in a postmortem study of Malawian children dying with a clinical diagnosis of cerebral malaria, 24% had other causes of death (8). This lack of specificity is problematic for clinical and pathogenesis studies. The increased specificity accorded by recent descriptions of retinal changes in cerebral malaria should address this issue (9).

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Abbreviations: BBB, blood brain barrier; CSF, cerebrospinal fluid; EMPs, endothelial microparticles; PPEPM-1, *Plasmodium falciparum* erythrocyte membrane protein-1; pRBCs, parasitized red blood cells; TBI, traumatic brain injury

Table 1. Neurocognitive sequel of cerebral malaria

Type of sequel	Sequel on discharge	Long-term sequel
Motor	Spasticity (hemiplegia, quadriplegia, or quadruplegia), cranial nerve palsies, and central hypotonia	Spasticity (hemiplegia, quadriplegia, or quadruplegia) and cranial palsies. Central hypotonia mostly resolves
Movement disorders	Ataxia, tremors, and dystonia	Dystonia. Ataxia and tremors resolve
Visual impairment	Blindness and milder degrees of visual impairment	Most visual impairment resolves
Speech and language impairments	Aphasia	Aphasia, impairments in pragmatics (use of language), receptive and expressive language, word finding, content, vocabulary, and phonology
Cognitive deficits	Impairments in working memory, attention, and learning	Impairments in attention, executive function and working memory, nonverbal functioning, and learning
Epilepsy	Generalized tonic clonic seizures and secondarily generalized seizures	Mostly generalized tonic clonic seizures and secondarily generalized seizures
Behavior difficulties and neuropsychiatric sequel		Attention difficulties, impulsiveness and hyperactivity, conduct disorders, self-injurious and destructive behavior in children, and the postmalaria neurological syndrome (acute psychosis, inappropriate speech and behavior, hallucinations, catatonia, and convulsions) in adults

The clinical hallmark of cerebral malaria is coma. This is thought to be caused by parasitized red blood cells (pRBCs) sequestered in cerebral microcirculation, but other authors attribute the impaired consciousness to metabolic factors and inflammatory mediators (10). In African children, coma develops suddenly with seizure onset often after 1–3 d of fever. A few children develop coma after progressive weakness and prostration. Brain swelling, intracranial hypertension, retinal changes (hemorrhages, peripheral and macular whitening, vessel discoloration, and/or papilledema) and brainstem signs (abnormalities in posture, pupil size and reaction, ocular movements, or abnormal respiratory patterns) are commonly observed. Other systemic complications such as anemia, metabolic acidosis, electrolyte imbalance, hyperpyrexia or hypoglycemia, and shock are commonly present. The prognosis is grave in deeply comatose patients with severe metabolic acidosis, shock, hypoglycemia, and repeated seizures.

In adults, cerebral malaria is part of a multiorgan disease. Patients develop fever, headache, body ache, and, progressively, delirium and coma. Compared with African children, seizures, papilledema, and retinal changes are less common and coma resolution is slower. Anemia, hemoglobinuria, jaundice, shock, renal failure, lactic acidosis, abnormal bleeding, pulmonary edema, and adult respiratory distress syndrome may develop. Some develop cortical infarcts and cerebral venous or dural sinus thrombosis as part of a disordered coagulation. Bacterial coinfection may be observed, particularly in those with shock, and accounts for the majority of late deaths (5,6).

Outcome

Without treatment, cerebral malaria is invariably fatal. In children, parenteral antimalarials (cinchonoids or artemisinin derivatives) are indicated, but even with this treatment, 15–20% die. However, in adults, mortality was lower if patients were treated with i.v. artesunate (11). This treatment is currently being evaluated in African children.

Earlier studies suggested that surviving patients fully recover (12), but over the past 20 y, it became clear that many children sustain significant brain injury; 11% are discharged with gross neurological deficits (13,14). Although some gross

deficits such as blindness, ataxia, and central hypotonia improve with time (15), 25% have long-term impairments especially cognition, motor function, or behavior impairments and epilepsy develops in 10% (15–18), Table 1. The prevalence (<5%) and pattern of neurological deficits are different in adults. Thus, other than causing thousands of deaths, cerebral malaria is now considered a leading cause of neurodisability in African children. The main risk factors include repeated seizures, deep and prolonged coma, intracranial hypertension, and hypoglycemia.

MECHANISMS OF BRAIN INJURY IN CEREBRAL MALARIA

The mechanisms of neural injury in cerebral malaria are poorly understood. Although the pathogenesis of cerebral malaria is incompletely understood, an insight into it can provide leads to the mechanisms of brain injury. In addition, descriptions of the prognostic factors for neurocognitive sequelae and postmortem studies have provided some understanding. However, three observations raise the following questions: 1) how does a largely intravascular parasite cause so much neuronal dysfunction? 2) despite the large number of parasites in the brain of most patients, why is coma so rapidly reversible with treatment and with very little demonstrable tissue necrosis? and 3) despite similar presentation, why do some children have a poor neurological outcome while others improve with hardly any deficits?

A fundamental problem in assessment of cerebral malaria pathogenesis is the relative paucity of CNS pathologic or physiologic data in humans. Because invasive testing of brain tissue is not safe, available data are largely from autopsy studies. However, these studies are limited in sample size and cannot address potential differences in survivors when compared with patients who die. Given this limitation, the majority of pathogenesis studies have been conducted in animal models, particularly murine models involving C57BL/6 or CBA mice infected with *P. berghei* ANKA. Although they have provided a wealth of information, important differences in what is known of pathogenesis in humans compared with

mice suggest that direct extrapolation of findings to human cerebral malaria may not be appropriate (19).

Parasite Sequestration in the Brain

Parasite sequestration in cerebral microvasculature is thought to be a central factor in pathogenesis and the resulting pathophysiological changes in tissue around the sequestered parasites, which may explain why an intravascular parasite may cause neural dysfunction and why some patients may have a poor outcome. Clearly, there are other factors because sequestration is also observed in patients dying of other complications of falciparum malaria (20).

Sequestration results from adherence of pRBCs to the endothelial lining (cytoadherence) using parasite-derived proteins exposed on erythrocyte surface (21). A group of parasite antigens including *Plasmodium falciparum* erythrocyte membrane protein-1 (PfEMP-1) mediate binding to host receptors of which intercellular adhesion molecule-1 (ICAM-1) is the most important and whose expression is up-regulated in areas adjacent to sequestered parasites. The sequestered parasite mass is further increased when adherent erythrocytes agglutinate with other pRBCs, form rosettes with nonparasitized erythrocytes, or use platelet-mediated clumping to bind to each other. Sequestration impairs perfusion and may aggravate coma through hypoxia. Furthermore, the ability of pRBCs to deform and pass through the microvasculature is decreased (22). Therefore, hypoxia and inadequate tissue perfusion may be major pathophysiological events. Although a critical reduction in metabolite supply (oxygen and glucose) may occur, in the majority of children, significant neural tissue necrosis is unlikely because with specific antimalarial treatment, coma is rapidly reversible. However, in the presence of increased metabolic demand such as during seizures and fever, the risk of neural injury is higher and may be worse if the patient is hypoglycemic (23) or if blood flow is further compromised by intracranial hypertension (24).

Cytokines, Chemokines, and Excitotoxicity

Cytokines and chemokines play a complex role in pathogenesis and have both protective and harmful effects. Parasite antigens released at schizogony trigger the release of both pro- and anti-inflammatory cytokines. Although the balance between these mediators is critical for parasite control, their role in pathogenesis of the neuronal damage is unclear. TNF, the most extensively studied cytokine in cerebral malaria, up-regulates ICAM-1 expression on the cerebral vascular endothelium increasing the cytoadhesion of pRBCs. Near areas of sequestration, there is increased local synthesis. The timing of this is important because early in disease, TNF may be protective but prolonged high levels contribute to complications (25). TNF is also involved in regulating synaptic transmission (strength, scaling, and long-term potentiation) (10). Thus, cytokine-mediated synaptic changes may contribute to the syndrome of cerebral malaria. Despite the prominence of TNF in pathogenesis, pentoxifylline, which decreases macrophage TNF production (26,27) and MAb to TNF (28), failed to decrease mortality.

Several other cytokines and chemokines are important, and in particular, interleukin (IL)-1b, IL-6, and IL-10 (29), but low levels of the chemokine RANTES are independently associated with mortality (30). The role of NO is controversial. The association between NO activity and inducible NO synthase with pathogenesis has been inconsistent (31,32). NO is involved in host defense, maintaining vascular status, and neurotransmission and is thought to be an effector for TNF. It is suggested that inflammatory cytokines up-regulate inducible NO synthase in brain endothelial cells leading to increased NO production. NO can cross the blood brain barrier (BBB), diffuse into brain tissue, and interfere with neurotransmission and therefore may partly be responsible for the reversible coma (33).

Other inflammatory products such as the metabolites of the kynurenine pathway—quinolinic and kynurenic acid—may also be important in pathogenesis. Quinolinic acid is a NMDA receptor agonist and an excitotoxin. It causes seizures in animal models of brain disease, whereas kynurenic acid is an antagonist and is generally thought of as neuroprotective. Excitation by quinolinic acid may contribute to convulsions in cerebral malaria. In children, there are graded increases in cerebrospinal fluid (CSF) concentration across outcome groups of increasing severity (34) although in adults, increased levels were associated with impaired renal function (35). Because of the role of NMDA receptors in modulating neurotransmission and as agonists, high levels of quinolinic acid may have long-term deleterious effects on cognitive function.

Endothelial Injury, Apoptosis, BBB Dysfunction, and Intracranial Hypertension

Cytoadherence of pRBCs to the endothelium initiates a cascade of events beginning with the transcription of genes involved in inflammation, cell-to-cell signaling, and signal transduction, which result in endothelial activation, release of endothelial microparticles (EMPs), and apoptosis of host cells (36). There is widespread endothelial activation in vessels containing pRBCs, and compared with other complications of falciparum malaria, significant increases in circulating EMPs are seen in patients in coma (37). In addition, interactions between pRBCs and platelets (which produce platelet microparticles) cause further injury to endothelial cells through a direct cytotoxic effect (38). Repair of the injured endothelium is also impaired as there is failure to mobilize sufficient circulating endothelial progenitor cells (39), and plasma levels of endothelial regulators, angiotensin-1 and angiotensin-2, are altered (40).

In murine models, apoptosis is first observed in endothelial cells and then in neurons and glia (41); the stimulus being contact of pRBCs with the endothelium (42) (Fig. 1). There is accumulation of activated/effector CD8 lymphocytes. Apoptosis may be induced through a perforin-dependent process, because cerebral symptoms are not seen in perforin-deficient models but only in wild forms that show high increases in perforin mRNA (43). Four patterns of axonal injury have been described: single axons, diffuse or more focal parenchymal

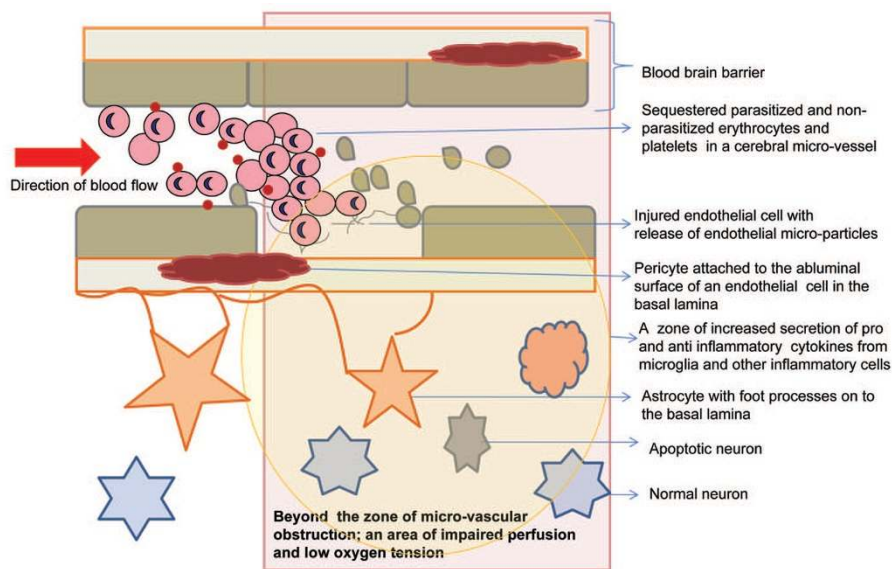


Figure 1. Changes in and around a cerebral microvessel with sequestered *Plasmodium falciparum* parasites. A schematic diagram showing changes in and around a cerebral vessel with sequestration of pRBCs. Cytoadherence of parasitized erythrocytes to the endothelial cell lining and sequestration of parasitized and non-parasitized cells in the cerebral capillary or postcapillary venule initiates an inflammatory process, endothelial activation, release of EMPs, and apoptosis in the exposed area. At the site of cytoadherence, the BBB is possibly disrupted, and there is an increased inflammatory response in the perivascular area with an increased release of proinflammatory cytokines.

patches and neuronal cell bodies (44), and axonal injury correlated with plasma lactate and depth of coma. Axons in children seem to be more susceptible to injury because the median CSF microtubule-associated protein *tau* level is 3-fold greater than in adults (45). The increased susceptibility to injury may explain the higher prevalence of sequelae in children.

Perivascular macrophages around vessels with parasites express receptors such as sialoadhesin normally present only if there has been contact with plasma proteins (46). Although disruptions at sites of sequestration can expose neurons to plasma proteins, significant leakage of plasma proteins into perivascular spaces has not been seen (47). Despite this, intracranial hypertension is common in African children; up to 40% of children with deep coma have brain swelling on computerized tomography scans (48). BBB dysfunction may contribute to the hypertension, although increased cerebral volume could be caused by sequestration and increased cerebral blood flow from seizures, hyperthermia, or anemia.

Intracranial hypertension reduces cerebral perfusion pressure, nutrient and oxygen delivery and can lead to global ischemic injury, herniation, brainstem compression, and death (24,49). Ischemic injury is seen on acute computerized tomography, and pattern of injury is consistent with a critical reduction in perfusion pressure (48). The convalescent scans in these patients show cerebral atrophy. Many children with severe hypertension are discharged with spastic quadriplegia and, subsequently, severe learning disability (24).

Cerebral Blood Flow and Perfusion

Patients with cerebral malaria have an increased cerebral blood flow. This increase is probably an adaptive response to high a metabolic demand to match oxygen and nutrient delivery to requirements because jugular bulb venous oxygen saturation remains within normal (50). However, recent studies of the retina have provided evidence for decreased local perfusion (51,52). In the eye, multiple discrete areas (100–1000 μm) of retinal whitening are observed in most children

with cerebral malaria. These areas have impaired capillary perfusion on fluorescein angiography (51), Figure 2. Physiologically, reduced local perfusion is associated with an abnormal electroretinograph (52). If the retina mirrors events in the brain, similar obstruction may be present in the brain, and coma in cerebral malaria may partly be a result of underperfusion in multiple but small areas of the brain. Because the patches of brain affected are small, with early treatment and rapid relief of obstruction, there is minimal tissue necrosis and early restoration of perfusion may explain the near complete recovery of gross neurological function in the majority of patients. However, exposure to hypoxia still leaves many children with subtle (*e.g.* cognitive) deficits. In those who die or develop severe brain injury, the sequestered mass may be higher, blood flow obstruction not readily reversed, and hypoxic and ischemic injury more widespread (53).

Regional blood flow may also be altered. In a transcranial Doppler study, sonographic abnormalities were associated with lateralizing deficits in six of 11 children who developed severe functional deficits on recovery (54), whereas in patients with severe intracranial hypertension, a linear relationship between cerebral perfusion pressure and blood flow velocity was observed suggesting that autoregulation was impaired. In addition, sonographic features suggesting progressive intracranial hypertension were seen in some who later died.

Seizures

Plasmodium falciparum is epileptogenic, and the risk of seizures increases with parasitemia (55). Seizures are a common feature of childhood cerebral malaria; >80% are admitted with seizures and seizures recur in 60% during admission (56). In other models, irreversible neuron damage is described after prolonged seizure activity; within days, edema is recognized on MRI (57) but overtime, this is replaced by local atrophy and gliosis (58). However, there is no consensus as to whether seizures cause the brain injury or are a manifestation of an injured brain (59,60). Thus, although prophylactic anti-convulsants in traumatic brain injury (TBI) prevented imme-

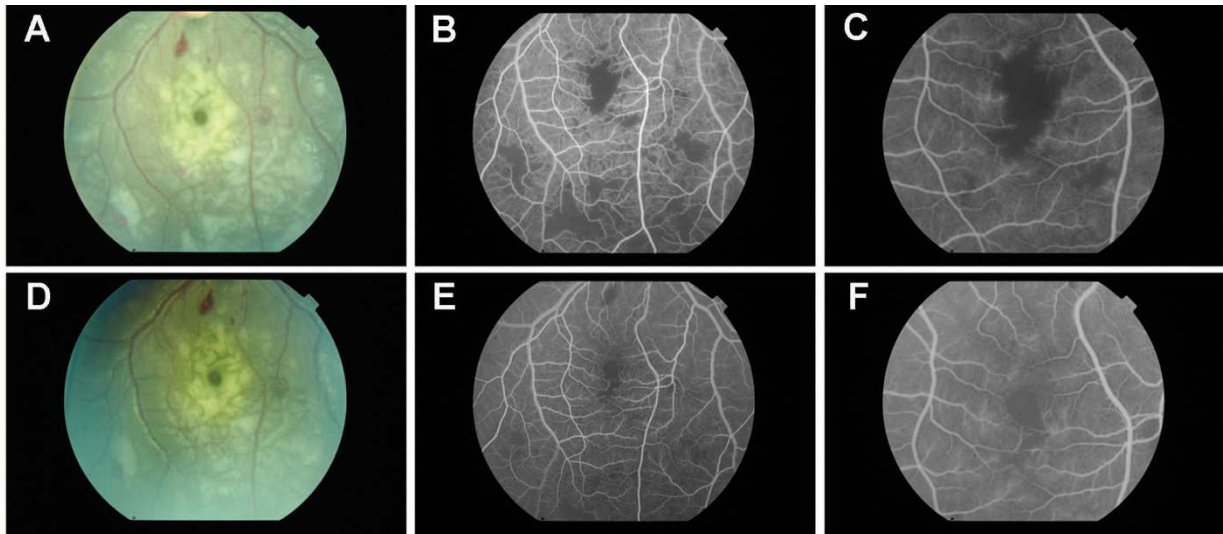


Figure 2. Retinal changes and fluorescein angiography in a child with cerebral malaria. Day 1 (admission is d 0): (A) Color fundus photograph of a child with cerebral malaria; multiple retinal hemorrhages are visible. No major change from admission. (B) Fluorescein angiography shows multiple areas of retinal nonperfusion. These are more clearly delineated than on d 0 (admission). (C) At higher magnification and later in the angiography run, there is some mild leakage round the border of the perfused and nonperfused zones. The leakage may suggest dysfunction of the blood-retina barrier. Day 3 of coma: (D) There is little change in appearance when compared with d 1. (E) But there is substantial recovery in areas of nonperfusion. (F) At higher magnification and later in the angiography run, leakage of fluorescein from reperfused capillaries, and capillaries previously on the border of nonperfusion is still observed. Photographs courtesy of Dr. Nicholas Beare—Royal Liverpool University Hospital and the Wellcome Trust—Liverpool School of Hygiene and Tropical Medicine Program in Malawi.

diate seizure recurrence, they did not reduce the risk of subsequent epilepsy (61). Similarly, high-dose prophylactic Phenobarbital in children with cerebral malaria significantly reduced seizure recurrences (62) but did not improve cognitive outcome (63). However, in this study, prophylactic Phenobarbital was associated with increased mortality (from respiratory depression) and the cognitive outcome study included only half of the original cohort. The likely scenario is that brain injury is caused by the seizure initiating noxious agent. Prolonged seizures may worsen this injury and setup a vicious circle of neural injury and more seizures.

Depth, Duration, and Cause of Coma

It has been suggested that cerebral malaria is not a single homogenous syndrome rather four distinct groups: a prolonged postictal state, covert status epilepticus, severe metabolic derangement, and a primary neurological syndrome (64). The fifth group may be patients with false cerebral malaria in whom coma has other causes and parasitemia is incidental (8).

Patients with prolonged postictal state have coma secondary to seizures, regain consciousness within 6 h, and have a good neurological recovery. Although the seizures are different from simple febrile seizures, the same risk factors may be at play. On the other hand, those with covert status epilepticus present with coma after prolonged seizures. The physical signs of seizure activity are often so minimal that they may not be recognized. Failure to detect the state can be disastrous because these patients are hypoxic and hypercarbic from hypoventilation and at risk of aspiration. The neurocognitive outcome may depend on how long the seizures have lasted.

Patients with severe metabolic derangement may regain consciousness a few hours after resuscitation. Impaired con-

sciousness is a secondary phenomenon to an unfavorable environment. Again, prolonged periods of either hypoglycemia or acidosis may cause neuronal dysfunction or death and, outcome may depend on duration of exposure among survivors.

Death and neurological sequelae may arise from different mechanisms. In Gambian children, neurological sequelae were associated with repeated seizures and with deep and prolonged coma, whereas death was associated with hypoglycemia and acidosis suggesting that most early deaths in cerebral malaria may result from an overwhelming metabolic derangement (65). Early correction of these derangements may buy time for definitive treatment. Recent phase II trials of albumin as a resuscitative fluid have supported this assertion (66) and have led to the on going Fluid Expansion as Supportive Therapy trial for very sick children in several African hospitals.

Patients with a primary neurological syndrome present with seizures often without severe metabolic disturbances and have the worst neurocognitive outcome. They are not severely anemic, and coma persists for 24–48 h well beyond the resolution of seizures. Intracranial hypertension is common. Coma may be a primary consequence of intracranial sequestration of malaria parasites.

Pathogenesis of Some Specific Impairment

Cognitive sequelae. In a prospective study, long-term cognitive impairment was described in 25% of children (18). Retrospective studies had documented rates of 14–24% (17,67). Risk factors for cognitive impairment included hypoglycemia, seizures, depth and duration of coma, and hypoflexia (18,23,67,68). Only one study has investigated the immunopathogenesis of cognitive impairment (29). In this

study, serum levels of multiple cytokines and chemokines did not correlate with impairment 6 mo after discharge, but CSF levels of TNF correlated with working memory and attention suggesting that elevated levels of CNS TNF adversely affects long-term cognitive outcome. The paucity of literature on risk factors for cognitive impairment highlights the need for additional studies in this area.

Speech and language impairment. Cerebral malaria is a leading cause of acquired language disorder in the tropics; 11.8% of surviving children have deficits especially in vocabulary, receptive and expressive speech, word finding, and phonology. Most deficits are observed in a subgroup of children some of whom have concurrent impairments in nonverbal functioning, memory, or attention (69). The pathogenesis is poorly understood; it is unclear whether the language deficits are part of a global injury or severe malaria causes injury to specific language centers. Studies with functional imaging may be useful in delineating pathogenesis.

Epilepsy. Epilepsy develops in ~10% of exposed children months to years after exposure (16), and the cumulative incidence increases with time (70). Although seizures in cerebral malaria occur in the context of a febrile illness and many have complex features, temporal lobe epilepsy is uncommon; instead, mostly generalized tonic-clonic and secondarily generalized seizures are observed (71). The pathogenesis of epilepsy is poorly understood although it may be a consequence of focal hypoxic/ischemic injury in border-zone areas of cerebral circulation (56,72) or global ischemic injury (48,72).

Recent concepts of epileptogenesis hypothesize that in patients exposed to brain injury, multiple areas of hyperexcitable networks each with different seizure probability and independent discharges may develop in the brain. Clinical seizures may develop when these discharges coalesce and involve more of the surrounding normal brain (73). This concept has been studied in animal models and in patients with intractable temporal lobe epilepsy in whom there is extensive neural cell loss, gliosis, axonal sprouting, and formation of new synapses in the hippocampus. Surviving neurons and glia express genes encoding ion channels and receptors—changes thought to be responsible for the altered physiologic features of the injured region (74). If the concept is true, in cerebral malaria, hypoxic/ischemic neural injury in areas of nonperfusion may be the casual mechanism.

Behavior and neuropsychiatric disorders. In children, behavior problems include inattention, impulsiveness and hyperactivity, conduct disorders, and impaired social development. Obsessive, self-injurious and destructive behaviors are also observed (17,55) (Richard Idro, personal observations). Symptoms develop 1–4 mo after exposure and the pathogenesis is unclear. In adults, the postmalaria neurological syndrome (Table 1) develops after parasites have been cleared (75). The pathogenesis is also unclear. Prospective studies are needed to describe these problems clearly, examine pathogenesis, and initiate therapeutic studies.

In summary, cytoadherence and sequestration of pRBCs in cerebral microvasculature initiate local endothelial injury and apoptosis, inflammation, BBB dysfunction, brain swelling,

and intracranial hypertension. Sequestration impairs local perfusion and may cause hypoxic injury. The noxious insults and epileptogenic parasites cause seizures which in turn may setup a vicious circle of brain injury and more seizures. Severe metabolic derangement may worsen the injury. The extent of brain injury may depend on causation of coma, degree of microvascular obstruction, and inflammatory response; duration of exposure, presence of concurrent complications such as shock, and availability and speed of interventions. To improve outcome, different mechanisms of injury may require separate interventions.

STRATEGIES FOR IMPROVED NEUROCOGNITIVE OUTCOME

Neuroprotective and Adjuvant Therapies

Brain injury after the exposure to noxious insult evolves over hours or days. This has raised the possibility that early intervention may limit injury. However, most neuroprotective interventions in man, particularly in TBI, have been disappointing. A poor understanding of pathophysiological mechanisms, properties of compounds used (*e.g.* appropriate therapeutic time window), patient selection, or choice of endpoints have been blamed for the failure (76). Studies in cerebral malaria have also been disappointing. These included interventions targeting elements of pathogenesis and risk factors for brain injury. Thus, there have been trials of steroids, immunoglobulin, acetyl salicylic acid, heparin, anti-TNF agents, mannitol, iron chelation, micronutrients, and prophylactic anticonvulsants. Because prophylactic Phenobarbital was associated with respiratory depression (62), there is an ongoing trial evaluating a less respiratory depressant prophylactic anticonvulsant, fosphenytoin.

More recent studies have examined the possibility of preventing endothelial injury or reversing rosetting and improving blood flow. In a murine model, administration of a low-molecular weight thiol, the B5 complex provitamin pantethine, prevented the development of cerebral malaria. Pantethine seemed to offer this protection by down-regulating platelet reactivity and release of microparticles from the activated endothelium. Attenuation of these processes left an intact BBB integrity (77). In another study, Glatiramer acetate, an immunomodulatory agent, was associated with a lower risk of cerebral malaria in treated animals (78). In both cases, human trials are awaited.

Two different anti-apoptotic approaches—treatment with z-VAD (a pan-caspase inhibitor) and overexpression of *Bcl-2* (a gene that prevents the release of apoptotic mediators from the mitochondria)—did not reduce cerebral malaria mortality in mice (79). However, the cytokine erythropoietin, which has anti-apoptotic, anti-inflammatory, vasodilating and neurotrophic properties, and widespread receptors in the brain, has shown greater promise. It crosses the BBB, and local synthesis is increased during hypoxia. Erythropoietin provided neuroprotection in animal models of TBI, infectious encephalopathy, and hypoxic ischemic encephalopathy (80) and offered protection against endothelial injury in the heart, causing NO-mediated coronary vasodilatation, increasing blood flow,

enhancing repair, and reducing apoptosis (81). In adults with stroke, high-dose erythropoietin reduced brain-infarct size and improved functional outcome (82). In mice with cerebral malaria, high-dose erythropoietin reduced mortality by 40–90%, (reviewed in Ref. 83) and in children, plasma levels $>200 \mu\text{L}$ were associated with $\sim 80\%$ less risk of sequelae (84). A phase I study of erythropoietin, $1500 \mu\text{kg}$, in children with cerebral malaria was recently concluded without any major concerns about the safety (85).

Heparan sulfate on endothelial cells mediates binding of pRBCs via DBL1 alpha domain of PfEMP1 (86). Interfering with this binding can potentially reduce parasite sequestration. Earlier studies of heparin and acetyl salicylic acid were not continued because they either failed to demonstrate sufficient evidence of benefit or because of toxicity. However, more recently, compounds with less anticoagulant effects have been developed. A Swedish group has recently completed a phase I trial of DFO2, a modified form of heparin with minimal anticoagulant activity, and plan to take this to phase II studies (Anna Vogt, personal communication).

Clearly, a poor understanding of pathogenesis is a major hindrance to progress in cerebral malaria research. MRI offers a way out including a noninvasive study of the structural, metabolic, biochemical, and functional features of the brain *in vivo* (87). A combination of time of flight angiography and diffusion-weighted imaging can describe obstruction to flow and the effects of obstruction in distal areas. Cerebral blood flow can be measured using arterial spin labeling while functional MRI can be used to describe neural activity in coma. In addition, proton MR spectroscopy can be used to measure levels of substrates and metabolites.

Rehabilitation

Because of the high mortality associated with cerebral malaria, few studies have focused on rehabilitation for children with sequelae. There are no guidelines to assess impairments or guide rehabilitation (88). With declining child mortality in the region and the growing number of exposed and therefore potentially impaired children, systems are needed to detect impairments and to develop and implement rehabilitation. Particular areas include physical and occupational therapy, behavior and speech therapy, cognitive rehabilitation, and hearing aids. A preliminary study of cognitive rehabilitation using a computerized program has demonstrated improved neuropsychological and behavioral outcomes in exposed children suggesting that similar interventions are possible (89).

CONCLUSION

Cerebral malaria causes brain injury in an unacceptable number of children. It is not a single and discrete syndrome; in different patients, coma develops through multiple mechanisms and there are several mechanisms of brain injury. Combinations of adjuvant therapies targeting specific mechanisms of brain injury may be needed to improve neurocognitive outcome. In the meantime, MR imaging may provide important insights into pathogenesis.

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