Pathogenesis of brain injury in cerebral malaria: emerging mechanisms and implications for intervention

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Purpose of review
Cerebral malaria (CM) in children has high mortality and leads to substantial long-term cognitive impairment. We review recent advances in defining the pathogenesis of brain injury in pediatric cerebral malaria.

Recent findings
The cascade of events leading to brain injury in pediatric CM includes blood–brain barrier (BBB) impairment due to local hypoxemia, ischemia, and endothelial activation after sequestration of infected erythrocytes; and oxidative stress after release of free heme. Tumor necrosis factor alpha (TNF-α), reactive oxygen species, CD8+ T cells and parasite toxins can then cross the impaired BBB and through activation of central nervous system immune responses and direct cytotoxicity lead to neuronal injury. Acute kidney injury and hyperuricemia may worsen BBB impairment and cerebral edema. Cytotoxic or vasogenic edema, abnormal blood flow states, and increased microvascular hemoglobin are present in pediatric CM, but their relationship to brain injury is not yet fully defined.

Summary
New studies of CM in children, including neuroimaging and electrophysiology studies, along with novel in vitro BBB model studies and ongoing experimental CM studies, show promise in improving our understanding of brain injury in CM and identifying interventions to decrease this injury.

Keywords
brain injury, cerebral malaria, children, neuronal injury, pathogenesis

INTRODUCTION

Cerebral malaria (CM), defined as coma in a child with *Plasmodium falciparum* parasitemia and no other identifiable cause for encephalopathy [1], is the deadliest form of *P. falciparum* infection, with case fatality rates ranging from 15% to 40% [2–4]. Children in malaria-endemic regions of Africa carry the highest burden of disease. Despite progress in control measures, including the deployment of two different malaria vaccines, the decline in mortality rates has plateaued since 2015 [5].

The clinical hallmark of CM, coma, reflects a dynamic disruption of blood–brain barrier (BBB) homeostasis and neural integrity. More than a quarter of children who survive CM have long-term neurologic or cognitive impairment [6,7], behavioral disorders [8], or mental health disorders [9]. The pathophysiology of brain injury that leads to these impairments has until recently been less well defined. We review recent advances in understanding the pathogenesis of brain injury in pediatric cerebral malaria, emphasizing studies identifying risk factors in affected children and emerging insights from neuroimaging, neurophysiological assessments, and novel in vitro models of the BBB.

MECHANISMS OF NEURONAL INJURY IN THE BRAIN MICROVASCULATURE

Central to the pathogenesis of human CM is sequestration of *Plasmodium falciparum*-infected red blood cells (*Pf*-iRBCs), a phenomenon in which PfEMP-1 proteins on *Pf*-iRBCs attach to brain microvascular

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Curr Opin Infect Dis 2025, 38:378–384
DOI:10.1097/QCO.0000000000001133

KEY POINTS

- Emerging studies are identifying key factors underlying brain injury and cognitive impairment in children with cerebral malaria (CM).
- The central pathogenic event in CM – sequestration of infected erythrocytes via PfEMP1-mediated binding to endothelial receptors – triggers local ischemia, hypoxia, and endothelial activation, leading to blood–brain barrier (BBB) dysfunction.
- Further BBB disruption is driven by elevated local tumor necrosis factor alpha (TNF-α) and oxidative damage from free heme.
- Neuronal injury may arise from ischemia and hypoxia and/or from TNF-α, reactive oxygen species, activated $CD8^+$ T cells, and parasite toxins crossing the impaired BBB, resulting in immune activation and neuronal cytotoxicity.
- Neuroimaging reveals both vasogenic and cytotoxic edema in children with CM, while vascular studies show abnormal cerebral blood flow patterns. Further research is needed to clarify how these changes contribute to brain injury.

endothelial cells via specific receptors, notably endothelial protein C receptor (EPCR) and intracellular adhesion molecule-1 (ICAM-1), and attract noninfected RBCs as well as white blood cells and platelets to the site, resulting in obstruction of the blood vessel in that area and local ischemia and hypoxia [10,11] (Fig. 1).

Sequestration in pediatric CM triggers tight junction disruption (delocalization of claudin-5, ZO-1, occludin), endothelial activation, and pro-inflammatory cytokine release, notably TNF-α, which serves to further upregulate binding of iRBCs to endothelial cells. Sequestration is further complicated by platelet clumping and fibrin deposition [12–15], and hemolysis of iRBCs that releases free heme, hemozoin, and toxic parasite byproducts, which can activate oxidative stress. Together, these factors lead to disruption of BBB homeostasis and increased barrier permeability. Activated endothelium and a damaged BBB may allow migration of pro-inflammatory cytokines such as TNF-α [16], parasite-derived toxins [17], and immune cells, including $CD8^+$ T cells [12], into the brain, contributing to local inflammation, inducing neuronal injury and contributing to cerebral edema (Fig. 1).

MECHANISMS OF NEURONAL INJURY IN THE BRAIN

Mechanisms in the brain that lead to neuronal injury and cognitive impairment in children with CM have not been extensively studied, because they require either brain tissue or cerebrospinal fluid (CSF) specimens, and some processes active at time of disease may not be detectable in stored and fixed tissue samples. Elevated CSF levels of TNF-α [16,18] and kynurenine [19] are associated with persistent long-term cognitive impairment. Both factors have also been associated with neurological damage in experimental cerebral malaria (ECM) model [20,21]. $CD8^+$ T cell migration into the brain, a key factor in ECM pathogenesis, was recently shown to be present in children who died of CM [12]. Further data on factors in the human central nervous system (CNS) related to brain injury in CM is needed. Noninvasive methods of assessment of CNS anatomy and physiology, such as MRI and EEG testing, and in vitro studies simulating the human BBB may help to fill this research gap.

SYSTEMIC CONTRIBUTORS TO CENTRAL NERVOUS SYSTEM NEURONAL INJURY

Acute kidney injury, a common complication in children with CM, is strongly associated with long-term cognitive impairment in children with CM [22]. Children with CM and acute kidney injury (AKI) have increased CSF markers of oxidative stress, the neuroexcitatory metabolite kynurenine, and neuronal injury, suggesting that AKI may affect CNS factors associated with neuronal injury and cognitive impairment, and highlighting the kidney–brain axis as a likely contributor to neurologic injury in CM [23].

Increased phenylalanine has been associated with slower coma recovery and worse Blantyre Coma Scores [24], and increased glycine and asparagine with worse long-term attention, in children with CM [25], suggesting that changes in amino acid levels may contribute to the risk of brain injury in CM.

Elevated UA levels, driven by purine catabolism during hemolysis of *Pf*-iRBC and reduced renal clearance, were recently shown to independently predict mortality and long-term cognitive impairment in children with severe malaria [26▪▪]. Hyperuricemia (UA >7 g/dl) also correlated with increased CSF levels of markers of oxidative stress, neuronal injury, and kynurenine in children with CM. High UA levels induce endothelial cell dysfunction in in vitro models [27] and increase BBB permeability and exacerbate neurological injury in rat models of stroke or traumatic brain injury [28], providing biological plausibility for the exacerbation of brain injury in pediatric CM by hyperuricemia. The findings suggest that UA may represent both a biomarker and a therapeutic target for brain injury in pediatric CM.

The APOE4 allele is a risk factor for development of CM and mortality in CM, but is paradoxically

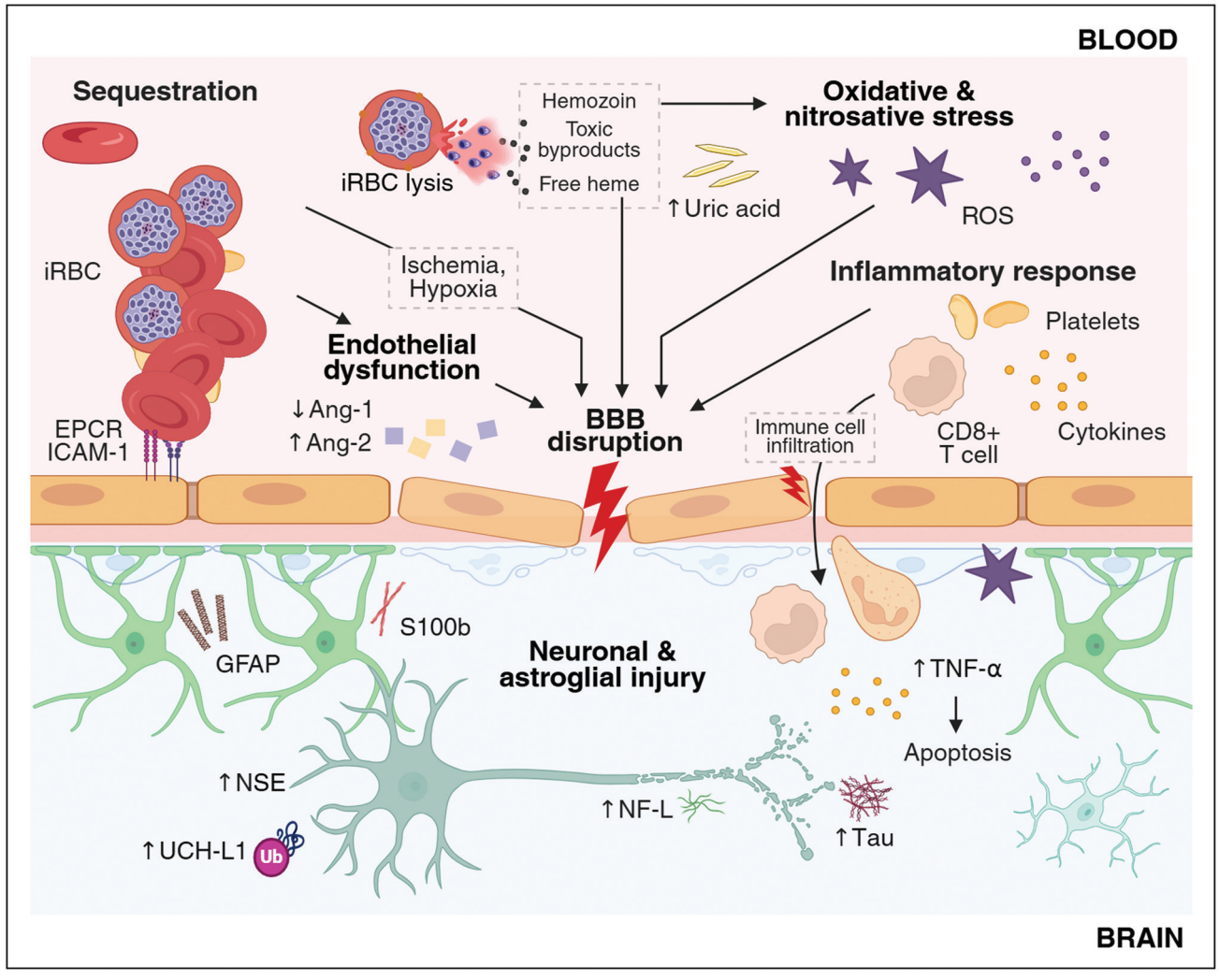

FIGURE 1. Blood–brain barrier interactions in cerebral malaria that may lead to neuronal injury. Ang-1/2, angiopoietin-1/2; BBB, blood–brain barrier; EPCR, endothelial protein C receptor; GFAP, glial fibrilliary acidic protein; ICAM-1, intracellular adhesion molecule-1; iRBC, *P. falciparum*-infected red blood cell; NF-L, neurofilament light; NSE, neuron-specific enolase; ROS, reactive oxygen species; S100b, S100 calcium-binding protein B; TNF-α, tumor necrosis factor-α; Ub, ubiquitin; UCH-L1, ubiquitin C-terminal hydrolase-L1.

associated with improved long-term cognition in children <5 years of age who survived CM [29]. This allele may modulate the inflammatory response and lipid-mediated neuronal repair, underscoring the complexity of host-pathogen interactions in determining outcomes.

CENTRAL NERVOUS SYSTEM AND SYSTEMIC BIOMARKERS OF BRAIN INJURY

Admission CSF levels of the neuronal injury biomarker tau in children with CM are associated with risk of long-term neurologic deficits and cognitive impairment [30] and plasma levels of tau [31] and the neuronal injury markers ubiquitin C-terminal hydrolase-L1 (UCH-L1) and neurofilament light chain (NF-L) are associated with BBB dysfunction, in-hospital mortality, and long-term cognitive impairment [32▪]. These biomarkers offer noninvasive tools that may allow early identification of children with CM at risk of long-term cognitive impairment.

EXPERIMENTAL CEREBRAL MALARIA MODELS: BENEFITS AND LIMITATIONS

Murine experimental cerebral malaria (ECM) models use *P. berghei* ANKA, which does not display *PfEMP-1* antigens and therefore does not lead to sequestration, the hallmark characteristic of human CM. Nonetheless, ECM studies have shown several

similarities to human CM, for example, free heme and oxidative stress leading to endothelial injury and BBB disruption [33], elevation of CNS TNF-a and kynurenic acid [34], and the presence of brain swelling and ring hemorrhages [35]. However, a number of features in human CM, including *Pf*-iRBC PfEMP-1-induced sequestration, and the associations of acute kidney injury [22] and hyperuricemia [26▪▪] to cognitive impairment are either not present or little studied in ECM. Conversely, some factors that dominate ECM, for example, the infiltration of $CD8^+$ T cells into the CNS, occur in children with CM [12], but are less prominent than in ECM. The limits of what can be studied in humans, and similarity of some findings in human CM and ECM suggest that ECM models may provide useful initial data on CM pathogenesis that can then be validated in human CM studies.

NEW INSIGHTS FROM NEUROIMAGING AND NEUROPHYSIOLOGY EVALUATION

Advanced neuroimaging has provided new insights into the spatiotemporal dynamics of brain injury. Serial magnetic resonance imaging (MRI) studies in pediatric and adult patients with CM reveal two predominant patterns of edema: cytotoxic edema, marked by restricted diffusion in hypoxia-sensitive areas like the basal ganglia and hippocampus, and vasogenic edema, indicative of BBB breakdown and increased extracellular fluid accumulation. In children, fatal CM is often associated with vasogenic edema, with severe brain swelling and brainstem herniation, whereas in adults, cytotoxic edema without overt swelling predominates [36]. The spatial distribution of these changes corresponds to regions implicated in long-term deficits, including memory and motor coordination. Imaging abnormalities may persist for months after treatment, underscoring that recovery of consciousness does not equate with absence of residual brain pathology.

Transcranial Doppler (TCD) ultrasound, a non-invasive technique, provides real-time cerebral hemodynamic data through measurement of cerebral large vessel blood flow velocities (CBFV). TCD assessments of critical closing pressure (CrCP) and diastolic closing margin (DCM) in children with CM showed that 36% of children with CM exhibited abnormally high or low CrCP, reflecting altered cerebrovascular tone, and that a DCM <20 mmHg, indicating a low perfusion reserve, was associated with significantly worse neurodisability outcomes. Abnormal CrCP and DCM suggest hemodynamic fragility in the CNS, potentially contributing to ischemic injury even when systemic blood pressure is preserved [37▪].

A study of children in Malawi with CM demonstrated that cerebral hemoglobin concentrations, as measured in the cerebral microvasculature by near-infrared spectroscopy (NIRS), were elevated in children with CM compared to children with uncomplicated malaria or healthy controls. These abnormalities correlated with MRI-defined brain swelling, suggesting that venous congestion may contribute to increased intracranial volume and pressure. The disordered microvascular hemoglobin dynamics captured by NIRS may reflect impaired cerebral blood flow autoregulation, a known contributor to brain injury in other forms of encephalopathy [38▪▪].

In a recent study, specific clinical electroencephalography (EEG) features – faster dominant background frequency and higher background voltage – correlated with better attention and memory outcomes in children <5 years of age with CM [39]. EEG electrophysiology studies may provide further insight into changes in neurotransmission pathways in acute CM and postepisode recovery.

Multimodal neuroimaging and physiologic monitoring are reshaping how CM-associated brain injury is detected, stratified, and understood. MRI and NIRS confirm that brain swelling arises from both vasogenic edema and vascular congestion, while EEG and TCD reveal functional and perfusion vulnerabilities that track with neurocognitive outcomes. These modalities underscore CM neuropathology's heterogeneous and dynamic nature and offer potential tools for early risk assessment in high-burden settings.

NEW INSIGHTS FROM IN VITRO BLOOD–BRAIN BARRIER MODELS

Dissecting the molecular and cellular mechanisms underpinning CM pathology has required in vitro systems that recapitulate the human neurovascular interface. Human-derived models using primary or immortalized endothelial monolayers have provided insights into parasite cytoadherence, endothelial activation, and BBB permeability. However, batch-to-batch variability, reduced barrier properties, and diminished expression and activity of tight junction proteins and efflux transporters reduce their translational capabilities. A new generation of human-based platforms that better simulate CM pathogenesis includes a human-induced pluripotent stem cell (hiPSC)-derived brain microvascular endothelial cell (BMEC) model co-cultured with iRBCs. This platform achieves trans-endothelial electrical resistance (TEER) values exceeding $1500\,\Omega\,cm^2$, mimicking in vivo-like BBB integrity. Upon exposure to *Pf*-iRBCs, the system demonstrated reduced TEER, disruption in the localization of tight junction proteins (occludin, ZO-1, claudin-5), and upregulation of ICAM-1

and VCAM-1, mimicking key features of endothelial activation observed in CM. This model provides a scalable, quantitative tool for testing adjunctive therapies to preserve BBB function [40▪▪].

Malaria pigment hemozoin (Hz) is a crystalline byproduct of heme detoxification released as parasites feed on hemoglobin within iRBCs. Hz is degradation resistant, allowing it to persist in tissues, contribute to sustained inflammation, induce oxidative stress, and contribute to endothelial activation and barrier dysfunction [13,17]. Studies of neuron or neuron and astrocyte cultures have shown that direct exposure of these cells to hemozoin led to metabolic dysfunction and decreased cellular viability [17], activation of stress-associated pathways, including MAPK signaling and DNA damage, and secretion of proinflammatory cytokines, including interleukin (IL)-1β, IL-8, and interferon gamma (IFN-γ) [41]. However, pediatric CM autopsy studies show that almost all hemozoin remains intravascular, so BBB model studies are needed to evaluate whether hemozoin in the vasculature can initiate these neurotoxic mechanisms [41].

A novel three-dimensional (3D) perfused human brain microvessel model was designed to support *in situ* maturation and adhesion of Pf-iRBCs under flow conditions. This system recreates key features of cerebral microvascular pathology, including flow-dependent cytoadherence, endothelial apoptosis at parasite adhesion sites, and spatially heterogeneous inflammatory responses. Notably, TNF-α exposure and iRBC perfusion triggered distinct transcriptional programs in endothelial cells, inducing inflammatory activation, junctional disruption, and localized binding and apoptosis. When combined, these stimuli produced compounded barrier injury, suggesting that parasite sequestration and host inflammation act synergistically to destabilize the BBB. The system enables high-resolution, temporal analysis of the endothelial response to malaria infection in a human-specific context, surpassing the limitations of flat monolayer and animal models [42▪▪].

In a mouse model and in vitro BMEC cultures, exposure to *P. falciparum* triggers Type I IFN signaling in BMECs, leading to immunoproteasome activation, enhanced MHC class I-mediated antigen presentation, and subsequent engagement of $CD8^+$ T cells [43]. Simultaneously, Type I IFN signaling impairs Wnt/β-catenin pathways, weakening TJ integrity and promoting barrier dysfunction. Immunological changes were associated with altered endothelial metabolism, as increased glucose uptake mediated Type I IFN signaling and downstream pathogenic effects. Blockade of glycolysis in vivo delayed CM onset and improved survival, supporting metabolic reprogramming as a potential therapeutic target.

These emerging experimental platforms represent a critical shift toward mechanistic fidelity modeling CM. They provide physiologically relevant tools for hypothesis testing and platforms for preclinical screening of therapeutic agents targeting specific cellular components of the neurovascular unit (NVU). However, challenges remain: few systems integrate neurons, glia, and perfused endothelium into a single platform, and long-term co-culture under dynamic conditions remains technically limited.

THE GOAL: ADJUNCTIVE THERAPIES TO DECREASE BRAIN INJURY IN CEREBRAL MALARIA

Despite the effectiveness of artemisinin-based therapies in reducing parasitemia, CM mortality and long-term cognitive impairment remain high, prompting investigation into host-directed adjunctive therapies aimed at stabilizing the vasculature and limiting brain injury. Numerous adjunctive therapies have been successful at reducing mortality in ECM models, but to date, none have reduced mortality in pediatric CM [44] and few have focused on the reduction of brain injury and cognitive impairment. Several potential interventions effective in ECM, including angiotensin receptor modulators, PPARγ agonists, BCR-ABL kinase inhibitors, and S1P receptor modulators [45,46], remain to be studied in humans. Ongoing or proposed studies in pediatric severe malaria or cerebral malaria include studies of hypertonic saline, mechanical ventilation, the glutamine antagonist 6-diazo-5-oxo-L-norleucine [47], and the heparin analogue sevuparin, which disrupts PfEMP1 binding to endothelial cells but has only modest anticoagulation effects [48]. Uric acid-lowering agents can potentially decrease brain injury in CM [26▪▪], and are being considered for study in human clinical trials.

CONCLUSION

In children with CM, a number of factors contribute to blood-brain barrier breakdown. The inciting event is infected RBC sequestration, which leads include local hypoxemia, ischemia and endothelial activation. Release of free heme causes additional endothelial dysfunction and oxidative stress. Cytokines (notably TNF-α), reactive oxygen species, $CD8^+$ T cells and parasite toxins can then cross the impaired blood-brain barrier, causing neuronal injury through oxidative stress, activation of the CNS immune system and direct cytotoxicity. Systemic factors, including acute kidney injury and hyperuricemia, may exacerbate this process. Within the brain, cytotoxic or vasogenic edema, abnormal blood flow states, and

increased microvascular hemoglobin occur, though further study is needed to evaluate how they relate to neuronal damage. New neuroimaging and electrophysiology studies, novel in vitro BBB models, and ongoing experimental CM studies together promise to improve our understanding of brain injury in CM and may lead to identification of therapies to prevent or decrease brain injury in CM.

Acknowledgements

The authors thank Caitlin Bond for her work in design of the figure for this manuscript.

Financial support and sponsorship

C.C.J. and D.D. received grant support from the National Institute for Neurological Disorders and Stroke (CCJ, R01NS055349; DD R21NS129234 and R21NS127215).

Conflicts of interest

There are no conflicts of interest.

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