

# An Overview of Cerebral Malaria: Lessons Learnt from Observations in Humans and Experimental Models

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## ABSTRACT

Malaria continues to be a serious public health problem killing 409,000 people annually worldwide, half of which come from 6 countries from sub-Saharan Africa. Out of 5 different species of malaria parasites, *Plasmodium falciparum* infection in humans is the main cause of mortality. It induces Cerebral Malaria pathology in 10-15% of affected individuals. Cerebral Malaria manifests as a neuropathological complication, leading to the disruption of the Blood Brain Barrier and significant neuronal damage that eventually causes coma and death in humans. Most of the clinical information about Cerebral Malaria in humans has come from postmortem examinations of the brain and therefore the use of experimental animal models became necessary. This provided valuable insight about the mechanistic processes that lead up to the induction of cerebral malaria pathology and also enabled screening and evaluation of therapeutic molecules for prevention of death. Unfortunately, till date no effective therapeutic interventions except artemisinin and quinine based therapies are available therefore understanding the different events that causes the pathology by learning from all the different observations obtained thus far, becomes of paramount importance.

**Abbreviations:** CM: Cerebral Malaria; WHO: World Health Organization; SM: Severe Malaria; MRI: Magnetic Resonance Imaging; MRS: Magnetic Resonance Spectroscopy; CT: Computational Tomography; PbA: *Plasmodium berghei* ANKA; BBB: Blood Brain Barrier; CNS: Central Nervous System; ECs: Endothelial Cells; ICAM-1: Intercellular Adhesion Molecule-1; VCAM-1: Vascular Cell Adhesion Molecule-1; EPCR: Endothelial Protein C Receptor; ECM: Experimental Cerebral Malaria; CS: Curdlan Sulfate; TNF: Tumour Necrosis Factor; BMS:  $\beta$ -Methasonehemisuccinate; GSK3 $\beta$ : Glycogen Synthase Kinase 3

## Introduction

Malaria has been a significant threat to human health throughout history. As an effective vaccine against malaria is not available yet vector control measures like the use of insecticide-treated mosquito nets and indoor residual spraying has received significant attention to prevent and reduce malaria transmission. According to the World Malaria Report, released on 30 November 2020, there were 229 million cases of malaria in 2019 resulting in 409 000 deaths annually world wide mostly affecting children under 5 years of age from 6 countries in sub-Saharan Africa [1]. Five different species of protozoan parasites belonging to the genus *Plasmodium* are capable of infecting humans and causing malaria

[2]. Out of these, two major species such as *P. vivax* and *P. falciparum*, are responsible for most of the morbidity and mortality in humans. The signs and symptoms that are seen in individuals who are infected and develop clinical signs of illness, varies widely between children and adults [3]. Malaria manifests itself by inducing the following types of conditions in humans - it may be accompanied by electrolyte and metabolic imbalances, respiratory failure, severe anemia, jaundice, pulmonary edema or a severe neuropathological condition termed as Cerebral Malaria (CM) [4]. The World Health Organization (WHO) defines CM as an unarousable coma that results from clinical manifestation due to *P. falciparum* infection in humans

when it is not attributable to other causes [5]. According to hospital admission records, 1–2 % of all *P. falciparum* infections result in CM, having a fatality rate of 10–20% [6]. Furthermore, at least 10 to 20% of those who survive and recover from CM suffer significant post-disease neurological sequelae for several years after cure [7]. In the regions of high malaria transmission, the age of the affected individuals and the degree of exposure to the parasite causing the infection are key determinants to the susceptibility to severe malaria. Developing complete immunity from malaria has not yet been possible for humans due to the complexity of the parasite's life cycle; however acquisition of clinical immunity, which confers protection from life-threatening illnesses are achievable. But the acquisition of clinical immunity requires numerous exposure to the parasite during an individual's life span through infective mosquito bites [8]. Most children, who get repeatedly exposed to malaria in areas of high transmission, acquire some form of resistance against the severe forms of the disease, provided they manage to survive the first few years of their lives after getting infected [8]. In areas of low transmission however, Severe Malaria (SM) occurs equivalently in all age groups, and is slightly more common in adults. This is because clinical immunity to malaria does not occur at all or takes a very long time to acquire and may persist for a short period. Although adults generally have a fairly good resistance against developing SM, infants are at an increased risk of developing malignant malaria, especially during their first years of life. However, the older children who've had at least a single prior exposure to *P. falciparum* infection, are disproportionately at risk of developing CM symptoms [9]. The epidemiology of CM is suggestive of the fact that the predisposition to disease manifestation or its prevention is ultimately determined not only by the virulence of the invading parasite; but is also attributable to the host's own immune response which contributes to the degree of disease pathogenesis and outcome [10-12].

### Clinical Attributes of the Pathology Observed in CM Patients

Post-mortem examination of human brain have helped to uncover the extent and type of brain pathology that occurs due to CM. leading to death. The prevalence of haemorrhages and swelling in the white matter of the subcortical rim and corpus callosum as well as presence of petechial and ring haemorrhages in cerebral and cerebellar cortices have been some of the most commonly reported findings from such examinations [13]. Histopathological analyses of brain of CM patients after death has revealed the presence of parasitized erythrocytes clogging the cerebral capillaries [13]. The pathologic features of CM also include the presence of monocytes and macrophages within cerebral vessels together with the sequestration of pigmented macrophages and parasitized erythrocytes confined to cerebral blood vessels [14]. Due to the lack of detailed comparative histopathological analysis, it is extremely difficult to determine the variations in CM

pathology between children and non-immune adults, but given the number of differences in the symptoms of pediatric and adult CM it is plausible that there may be some age-related variations in the cerebral pathology observed in these groups [15]. Although parasite sequestration, haemorrhages and inflammation are some of the common findings in histological analyses of the brains of the majority of CM patients, it is quite probable that CM is not a homogenous syndrome. In fact, three distinct and different patterns of histopathological changes have been observed in African children. Firstly, there is the 'classical' pattern with parasite sequestration, perivascular haemorrhages and immune cell infiltration observed within brain micro-vessels due to CM. Next, there are incidences where parasite sequestration has been observed within the brain, but without any of the other aforementioned abnormalities. And lastly, numerous cases have been observed where individuals with high peripheral parasitemia develop a syndrome that is clinically defined as CM but where there has been no evidence of parasite sequestration within the brain [16,17]. The reasons for the observed variations in pathology are not clear and are hard to elucidate with utmost clarity but investigations indicate that it may be attributable to genetic variations in either the hosts or the parasites or may be combination of both, along with external environmental factors and the differences in the intensity of the immune response mounted against the parasite to control the infection.

### The Limitations of Studies of Human Cerebral Malaria & Importance of Experimental Models in Animals

Cerebral Malaria arises as a result of a complex sequence of inter-related events that ultimately lead to the manifestations of the clinical symptoms observed in affected individuals. The sequestration of trophozoite infected Red Blood Cells (pRBC) in the small blood vessels together with the rupture of infected red blood cells and the release of parasite-derived toxins could all be the defining features that lead to the induction of the pathology associated with the development of CM [18,19]. The effects of systemic and local events including pRBC sequestration and breach, the activation of monocyte, endothelial, and glial cells, the release of harmful inflammatory substances, and the exact sequence of events with their individual timing that ultimately lead up to the disease manifestation are very much unknown when it comes to precipitating the pathogenesis of CM. Since the histopathological analysis of brains of CM patients can only be done after death during post mortem, it is extremely difficult to describe the factors that would have lead to the onset of the disease or the determinants for its abrogation when treatment would have been successful. Such investigations and comparisons are essential to delineate truly pathogenic systemic and intra-cerebral processes from neutral and/or protective responses. Increased utility of non-invasive *in vivo* imaging techniques, such as Magnetic Resonance Imaging (MRI) and spectroscopy (MRS) and Computational Tomography (CT), should hopefully help to address these issues,

but these studies are severely restricted by ethical constraints and the availability of the expensive specialized equipment in malaria-endemic areas [20-22]. In order to observe and understand the immunological pathways that are primarily elicited to control the infection together with the manipulations brought about at the level of the invading pathogen for its own survival and persistence, it is imperative to implement direct intervention studies and move beyond purely descriptive conjectures, which is an extremely difficult undertaking. Examination of the peripheral blood often provides very limited information about the immunological and parasitological environment in the brain as the peripheral blood parasitaemia does not accurately reflect total parasite biomass. Total parasite biomass is a stronger correlate of severe malarial disease than the peripheral parasitaemia [23]. The situation is made further complicated as the patients usually present themselves to the hospitals only when the disease has reached a very advanced stage. It is clear that other approaches – in combination with human studies – are required to fully understand the pathogenesis of CM. Much of our understanding of mammalian physiology has come from studies of animals and the extent of the conservation of basic immunological and neuropathological processes between laboratory rodents and humans has become more apparent [24,25]. Primate models of CM, including *P. knowlesi* and *P. coatneyi* infections in Rhesus monkeys and *P. falciparum* infection in squirrel monkeys [26,27], have allowed the investigation of some aspects of CM, but these models are prohibitively expensive and are done with smaller number of animals due to ethical reasons. neuropathological syndromes have been shown to develop in certain strains of inbred mice infected with various strains of *Plasmodium berghei* [28,29]. There has been and continues to be significant disagreement within the malaria research community as to whether the murine models share sufficient similarities with human cerebral malaria to make them relevant or useful. However, experimental models have proven invaluable for understanding the pathogenesis of numerous autoimmune and infectious diseases of humans and many vaccines and immuno-therapies currently in use were initially developed and tested in experimental models [25]. Therefore from that aspect, the use of relevant experimental animal models has significantly aided in the study of CM and are indispensable tools for gaining valuable insight and improving our understanding of the disease pathogenesis.

#### ***Plasmodium Yoelii* XL and *Plasmodium berghei* K173**

Although more extensively studied as a model of hyperparasitaemia and failure of parasite control, PyXL has been shown to sequester within the brain microvasculature and produce a cerebral syndrome in mice comparable with human cerebral malaria. [30-32]; however, the hyper-parasitaemia associated with this infection (rapidly ascending peripheral parasitaemia that can reach 80–100%) is not typical of human CM cases and this

model is not widely used to study CM. In a few studies, *P. berghei* K173 has been found to induce CM-like symptoms, but the dose-dependent onset of Experimental Cerebral Malaria (ECM) in this model (inducing cerebral pathology after low dose infection which does not happen when a high dose is used) also limits its utility as a model of human CM. *P. berghei* K173 parasite is frequently used to induce a non-ECM-infection to compare with the most widely used model of ECM involving *P. berghei* ANKA infection [33,34].

#### ***Plasmodium berghei* ANKA**

The *Plasmodium berghei* ANKA (PbA) model manifests many events seen during human CM and is accepted as the best available experimental mouse model of cerebral malaria. Infection of susceptible strains of mice, including C57BL/6 or CBA mice, leads to the development of fatal cerebral pathology, with clinical signs including ataxia, fitting, respiratory distress and coma [35,36]. The time to onset of clinical signs varies depending on the dose of parasite used for causing infection, the genetic background of the host and the specific clone of the infecting parasites, but is typically between 5 to 10 days post-infection [36]. As in humans, there is a rapid deterioration in the condition of infected animals once clinical symptoms set in, with death often occurring within 4 or 5 hr after the onset of neurological signs. Multiple areas of blood-brain barrier disruption with vascular leakage involving the cortex, cerebellum and olfactory bulb are observed in brains of PbA-infected mice displaying signs of ECM, with loss of specific neuronal cell populations within the cortex and striatum accumulation of pRBC within blood vessels and focal perivascular inflammation [37-39]. ECM is also associated with the significant accumulation of platelets within the brain vasculature [40]: platelets have been shown to directly promote endothelial cell damage during infection. Cognitive dysfunction in mice during *P. berghei* ANKA infection, as shown by impaired memory, is directly correlated with haemorrhage and inflammation, including microglial activation [41]. Indeed, the accumulation of monocytes and macrophages, and activation of brain resident mononuclear cells, including astrocytes and microglial cells is believed to be a key feature of ECM. As in humans, genetic and environmental factors determine the susceptibility of mice to ECM. For example, the resistance of F1 intercrossed BALB/c (resistant) and C57BL/6 (susceptible) mice to the development of ECM is determined by age, and environmental exposure, with young mice (8–10 weeks) susceptible to ECM and older mice (16–20 weeks) resistant to the development of cerebral pathology [41].

#### **The Involvement of Blood Brain Barrier in CM Pathology**

Several studies on patients in Africa and Asia have shown that the disruption of the Blood Brain Barrier (BBB) in CM leads to severe neurological complications including

1. Intracerebral hemorrhage,
2. Seizures resulting from electrolyte imbalance, and
3. Increase in intracranial pressure due to widespread edema resulting in axonal damage [42-45].

All of these factors ultimately result in Central Nervous System (CNS) dysfunction and death. The BBB is a semipermeable membrane that separates the peripheral blood from the brain parenchyma. The BBB comprises a monolayer of Endothelial Cells (ECs) joined together by tight junctions and the underlying basal lamina. The integrity of the BBB is further supported by pericytes and the astrocyte end-feet [46]. The BBB, together with microglia and neurons, forms the neurovascular unit. Apart from serving as an anatomical barrier, the BBB plays a crucial role in the homeostasis of the CNS by facilitating the transport of nutrients such as glucose and amino acids from the blood to the CNS and removal of metabolic waste products from the CNS into the blood by means of specific transport channels [46]. Up to now, the precise underlying mechanisms leading to the disruption of BBB integrity during CM have remained unclear. Several mutually nonexclusive events have been associated with BBB breakage in human and murine studies, namely

1. Sequestration of iRBCs to the brain ECs [47-49],
2. An excessive inflammation resulting from heightened intracerebral proinflammatory cytokine response [49],
3. Disseminated intravascular coagulation in the brain [50,51], and
4. Dysregulation of vascular ECs [52]. In addition, a growing number of reports implicate two other major factors in the disturbance of the BBB:
  - a) The host's pathway for tryptophan metabolism, also known as the kynurenine pathway, and
  - b) Extracellular vesicles released by the host and the parasite called microparticles.

Accumulation of parasitized erythrocytes to the luminal site of microvessel ECs triggers CM. The *P. falciparum* infected erythrocyte membrane protein-1 (PfEMP1) facilitates the adhesion of the infected erythrocytes to the brain vascular ECs. PfEMP1 is localized to small cup-like protrusions on the plasma membrane of infected erythrocytes called knobs, which mediate the binding of the iRBCs to the ECs [53]. PfEMP1 binds to various receptors on the brain ECs, including the intercellular adhesion molecule-1 (ICAM-1), the vascular cell adhesion molecule-1 (VCAM-1), and the cytokine-activated Endothelial Protein C Receptor (EPCR), thereby immobilizing the iRBCs on the vascular endothelium [54-56]. Patients with CM show an expansion of parasites expressing PfEMP1 that bind to both ICAM-1 and EPCR [57,58]. Platelets induce the

adhesion of iRBCs to one another, forming large autoagglutinates [59]. Furthermore, noninfected erythrocytes form rosettes around the iRBCs, contributing further to microvascular obstruction [59]. Since sequestration of iRBCs to the brain endothelium plays a critical role in the development of CM, prevention of sequestration and desequestration of the iRBCs are attractive therapeutic approaches, discussed in detail by Glennon, et al. [60]. The binding of PfEMP1 to the receptors on the ECs may trigger multiple signaling pathways in ECs, resulting in the reorganization of tight-junction complexes, ultimately leading to the leakiness of the BBB. *In vitro* studies on transendothelial migration of leukocytes, using human and murine ECs, have shown that engagement of ICAM-1 induces the phosphorylation of cytoskeleton-associated proteins, including FAK, paxillin, p130Cas, and cortactin, resulting in remodeling of the endothelial cytoskeleton to facilitate BBB opening [61].

### The Role of the Host's Immune Response in the Pathogenesis of CM

**Human Cerebral Malaria:** The aetiology of CM provides clear evidence for the involvement of the host immune response on the basis of a distinct pattern of cytokine profiles that are observed in individuals with CM. A high concentration of plasma TNF, IFN- $\gamma$ , IL-6 along with elevated ratios of pro-to anti-inflammatory cytokines are consistently observed in CM patients. High concentrations of inflammatory cytokines in the cerebrospinal fluid have been associated with a high risk of developing neurological sequelae [62]. Investigations have demonstrated that binding of pRBCs to brain endothelial cells, causes the activation of the NF- $\kappa$ B pathway, leading to the production of CCL20, CXCL1, CXCL2, IL-6 and IL-8 [63]. How these inflammatory responses lead to the onset of CM are still topics for discussion. It has been observed that the induction of high concentrations of pro-inflammatory cytokines lead to the upregulation of endothelial ICAM-1 and VCAM-1 expression, as well as enhanced expression of PfEMP1 on pRBCs [64]. It potentiates pRBC sequestration through the interaction of PfEMP1 with these cell adhesion molecules. Inflammatory cytokines may also be responsible for the presence of activated microglial cells the main phagocytic macrophage-like cell population of the brain, and sequestered monocytes in CM. It has been suggested that activated myeloid cells amplify the local intra-cerebral inflammatory response – by presenting antigens to T cells and/or producing inflammatory cytokines. However a defined exploration of this pathway that may lead to conclusive observations in human CM is not feasible. There are significant constraints in being able to access and study important anatomical sites at crucial time points in human patients during the onset of CM symptoms. The role of T cells in the pathogenesis of the disease is not well documented. The existing data only provides information pertaining to the differences in the T cell populations in the peripheral blood of CM and non-CM patients, making conclusive interpretation



of the available information very difficult [65]. Nevertheless, reductions in numbers of circulating CD4+ T cells (reflecting either sequestration in tissues or activation-induced cell death) and increased frequencies of CD4+ T cells expressing TCR Vb21.3 have been correlated with disease severity [66].

Similarly, the potential role of CD8+ T cells in mediating the observed pathology in CM has been very difficult to elucidate and there is no substantial evidence that definitively implicates the association of CD8+T cells with the development of CM pathogenesis. The most conclusive evidences for the involvement of the host immune responses to be associated with the precipitation of CM comes from studies undertaken to understand the role of genetic polymorphisms in individuals in determining the outcome of the infection [67]. The details of these associations vary from one population to another, likely reflecting differences in genetic background, but making it apparent that higher than average inflammatory responses increases the risk of development of CM. [68]. The idea that excessive pro-inflammatory immune responses pre-dispose to CM is also consistent with the clear age-related susceptibility to the development of CM in malaria endemic areas. The general observation is that very young children who are yet to acquire malaria specific cellular immune responses are relatively resistant to CM. These individuals present themselves with severe malarial anaemia instead of developing CM symptoms. In contrast, older children who are more likely to have primed Th-1-like adaptive immune responses because of prior exposure to malaria infections are at an increased risk of developing CM. Epidemiological investigations suggest that repeatedly exposed individuals eventually develop protective immunity, which may be characterized by the ability to control parasite replication by keeping parasite densities below the critical threshold for induction of hyper inflammatory immune responses to prevent pRBC sequestration and impede neurological damage [68,69].

**Experimental Cerebral Malaria:** The vast majority of the immunological features of human CM are recapitulated during *P. berghei* ANKA infection in susceptible mice. The susceptibility of various inbred mouse strains to Experimental Cerebral Malaria (ECM) has been directly correlated with the strength of the pro-inflammatory immune response to the parasite and to the response of microglial and cerebral endothelial cells to these inflammatory mediators [70,71]. Experimental manipulation of *P. berghei* ANKA-infected mice has allowed causal relationships to be established between specific immune responses and the development of ECM which are consistent with the associative observations in human studies. Administration of LPS, neutralization of IL-10 or heme oxygenase 1 or inhibition of CTLA-4 signalling during *P. berghei* ANKA infection all lead to the development of ECM in normally resistant mice, whereas ablation of pro-inflammatory cytokine and chemokine signaling or depletion of macrophages prevents the development of ECM in susceptible mouse strains [72,73]. Taken

together, the vast majority of experimental evidences indicate that the balance of Th-1 to T regulatory responses is critical in determining the eventual outcome of these infections [74]. The manipulation of Th-2 responses in these studies did not substantially affect the outcome of infection but lowering the aggravated Th1 responses has been associated with improvement in the disease outcome [75]. Similar to humans an increase in the circulating levels of pro-inflammatory cytokines in ECM susceptible mice activates the cerebral endothelium, leading to increased expression of cell adhesion receptors, as well as upregulating chemokine production and chemokine receptor expression on leukocytes. In contrast to human cerebral malaria studies, the role of CD8+ T cells in the development of ECM in mice is well established. It has been observed that CD8+ T cells accumulate in the brains of susceptible but not resistant mice, in a CXCR3-, IP-10- (CXCL9), MIG- (CXCL10) dependent manner.

These events have been observed to occur immediately before the onset of neurological signs and are believed to directly cause disruption of the blood-brain barrier due to endothelial cell damage via perforin production [76-79]. Depletion of CD8+ T cells either from the start of infection or later during infection has been studied to completely inhibit the development of ECM. More detailed investigations indicate that CD8+ T cells migrate to the brain in a largely antigen-specific manner, following cross-presentation of malaria antigens by classical CD8+ dendritic cells [80]. Studies performed to understand how CXCR3 upregulation on CD8+ T cells mediates migration of this cell population to the brain demonstrated that NK cell-derived IFN- $\gamma$  was required for their accumulation within the brain in susceptible mice. These observations reveal important information pertaining to the interactions between innate and adaptive immune responses in the pathogenesis of ECM, thus opening up potential new avenues of research into the role of innate immune responses, and of genetic variation in innate response genes, in the pathogenesis of human CM. In this context, effector CD4+ T cells were observed to provide help to CD8+ T cells in contributing to the development ECM as studies demonstrated that depletion of CD4+ T cells during the early (but not later) stages of *P. berghei* ANKA infection prevents the development of ECM [81]. In separate studies, however, depletion of CD4+ T cells during the later stages of infection also prevented the development of ECM, implying that although far fewer CD4+ cells accumulate in ECM brains in comparison to CD8+ T cells, making it apparent that CD4+ T cells may also be involved in ECM development, possibly mediating the effector phase of the disease pathogenesis. However, given the constraints of studying the exact sequence and interplay of different processes in humans, at present it is extremely difficult to definitively state whether the pathogenesis of CM in humans is more, or less immune mediated than what is observed in ECM in mice, and whether cells, such as CD8+ T cells, play comparable roles in the development of pathology in these two conditions. The ECM

the model provides valuable clues to plausible events that can lead to the development of pathology during malaria infection.

#### **Adjunctive Therapies For Management of CM Pathology:**

The major reasons for concern for CM in humans stem from the fact that the disease can develop rather suddenly, after just initial bouts of fever that lasts only for 2–3 days. The clinical symptoms associated with early-stage CM are not easily identifiable and is quite difficult to differentiate from encephalitis, meningitis and other febrile convulsions. This implies that the rapid and early diagnosis of the condition is often not possible, which delays the initiation of proper treatment. Coma is the standard definition of CM, but there are other symptoms associated with the condition that include general malaise, headache, fits, vomiting and diarrhea. The early symptoms of CM can progress rapidly to increased intracranial pressure, hemiparesis, ataxia and coma and if immediate medical treatment is not provided it increases the risk of treatment failure and mortality. The diverse set of neurological complications that are associated with CM indicate that multiple areas of the brain are affected by the condition. Since Malaria is a complicated disease and there is no effective vaccine yet to prevent the disease, anti-malarial drug-based therapies are the only avenues for patients who present themselves with the complication of cerebral malaria. However, the incidence of neurological deficiencies and mortality remain unacceptably high with fatality rates of around 15% following treatment with Artemisinin based combination therapies, compared with 20% for traditionally used quinine-based treatments. Given that anti-malarial therapy can only be implemented when CM is first suspected or diagnosed at health care centres; the risk from CM lies in the fact that the syndrome might already be at an advanced state in the majority of these individuals and anti-malarial drugs by themselves are often insufficient to reverse and alleviate the symptoms. At present the lack of understanding of the pathogenesis of CM hinders the identification of most efficacious targets for therapeutic interventions to be properly implemented.

Therefore, there is an urgent need to develop adjunctive therapies that can be administered with anti-malarials that can, both halt the progression of CM and also promote healing of brain dysfunction. Based on successful case reports corticosteroids were one of the first treatments proposed as an adjunctive therapy for CM with the aim of reducing swelling and inflammation in the brain. However, dexamethasone failed to demonstrate a decrease in mortality in two clinical trials [82]. Similarly, treatment with intravenous immunoglobulin resulted in increased deleterious outcomes compared to the placebo group, including higher mortality and more neurological sequelae in children [83]. The failure of this therapy was attributed to not being able to reverse cytoadherence and sequestration. Curdlan Sulfate (CS), a sulfated 1 → 3-β-D-glucan, a known inhibitor of *P. falciparum* *in vitro*, has also been tested due to its capacity to modulate the immune response to *P. falciparum* [84]. CS was expected to have some anticoagulant properties, and

confer certain direct and nonspecific effect on cytoadhesion and rosetting. However the studies failed to demonstrate differences in mortality, possibly because of small sample sizes, but CS was safe and appeared to reduce the severity of the disease process [85]. Since high circulating levels of TNF has been attributed to the severity of CM pathology, therapy targeting Tumour Necrosis Factor (TNF) and its effects have also been explored. However, no difference in mortality was shown and moreover, there was an increased risk of neurological sequelae in the experimental group [86]. The failure of this therapeutic approach was thought to be due to antibody mediated retention of TNF in circulation, [86]. A variety of therapies that target a number of different mechanisms have been tested in experimental mice models. In the case of ECM, the neurologic signs appear and intensify typically after day 5 post infection (p.i.) with *P. berghei* ANKA infections, and ECM progresses rapidly after that so that after day 5 p.i., mice show BBB dysfunction, brain swelling, and hemorrhaging and necropsy. Mice begin to die by day 6 p.i., and by day 12 p.i., nearly all mice succumb to the infection. One such study in ECM tested a new formulation of glucocorticosteroid, whereby β-Methasonehemisuccinate (BMS) was encapsulated in liposomes and when administered at a late stage of infection it improved survival and prevented the development and progression of the cerebral malaria syndrome [87].

Curcumin is a non-toxic, natural anti-inflammatory molecule found in *Curcuma longa* rhizomes that scavenges reactive oxygen and nitrogen species [88]. *In vitro* studies have shown that curcumin has additive anti-parasitic activity when used in combination with artemisinins and administered in combination with arteether to mice showing symptoms of ECM. Curcumin improved survival and prevented death by lowering inflammation and impeding damage to the BBB [88, 89]. Preclinical models have investigated the role of lithium as a potential neuroprotective intervention. Lithium has been proposed to act as a neuroprotective agent by its ability to inhibit glycogen synthase kinase 3 (GSK3β), activate the PI3 K/Akt and MAPK signalling pathways, and by inducing the expression of brain-derived neurotrophic factors in neurons [90]. Lithium chloride administered to mice with ECM significantly increased the activation of Akt, which was associated with the prevention of adverse neurocognitive outcomes. Adjunctive treatment with lithium chloride was associated with better spatial and visual memory, and motor coordination in mice recovering from ECM [91]. Targeting endothelial activation and preventing microvascular permeability and vascular leak in CM can be another potential target for adjunctive therapy [92]. The angiopoietin (Ang)-Tie2 axis critically regulates endothelial cell function [93]. Perturbation of Ang-1, Ang-2 and soluble Tie2 concentrations are associated with disease severity and death in CM in both murine models and humans [94]. A mechanistic role for the Ang- Tie2 axis was established in ECM, where it was shown that Ang-1-deficient mice were more susceptible to ECM and adjunctive administration

of a recombinant Ang-1 construct preserved BBB integrity and improved survival beyond artesunate monotherapy alone [94].

## Conclusion

Malaria remains a major global health problem, associated with high morbidity and mortality. Strategies have to be developed to improve early detection and recognition of cases so that immediate treatment can be made available in order to prevent progress of the disease towards the severe condition and prevent death. For those individuals who do progress to severe forms of the disease despite prompt treatment, new tools are needed to understand how to prevent neurocognitive deterioration in CM survivors. However so far, the majority of attempts to enhance the efficacy of anti-malarial drugs with adjunctive therapy have not been very successful. The development of effective therapeutic interventions would come from a more complete understanding of the physiopathology of the disease and learning from our experiences both in humans and experimental models. Further research is needed to improve our understanding of the disease process and implement feasible strategies for effective management of CM in humans.

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