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Review Article

Cerebral malaria: a lethal complication of a common tropical infection

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ABSTRACT

Cerebral malaria (CM) represents a deadly neurological complication associated with *Plasmodium falciparum* infection. It is defined as an unarousable coma or a deep level of unconsciousness in the presence of a *P. falciparum* parasitemia, the diagnosis confirmed after exclusion of other common causes of coma such as hypoglycemia, septicemia, metabolic derangements and bacterial and viral meningitis/encephalopathies. Mortality is high and some surviving patients sustain neuronal injury which manifests as long-term neuro-cognitive impairments. Microscopy of Giemsa-stained blood smears remains the gold standard for confirmation of malaria diagnosis. The purpose of this review was to summarize the updated knowledge on the disease, its presentation, complications and neurological sequelae and the presently available newer and experimental adjuvant therapies. For this review, a PubMed search was conducted for articles and case reports from 1968 to 2020 containing the keywords cerebral malaria, *P. falciparum*, neurological impairment, neurocognitive defects and artesunate combination therapy. The treatment includes specific antimalarial therapy, supportive therapy for multi-organ dysfunction and management of associated complications. Prompt and rapid stabilization of the patient, adequate fluid supplementation and correction of electrolyte imbalance remain the most vital supplementary interventions in these cases, along with early induction of primary parenteral antimalarial therapy in the form of artemisinin based combination therapy (ACT) or quinine. Neurological sequelae including seizures are frequently observed in many treated and recovered cases, with some patients having to endure long term neurocognitive defects.

Keywords: Artesunate, Cerebral malaria, Neurocognitive impairment, Parasitemia, *Plasmodium*

INTRODUCTION

CM represents a deadly neurological complication associated with *P. falciparum* infection. It is defined as an unarousable coma or a deep level of unconsciousness in the presence of a *P. falciparum* parasitemia, the diagnosis being made after exclusion of other common causes of coma such as hypoglycemia, septicemia, metabolic derangements and bacterial and viral meningitis/encephalopathies.[1] CM is one of the most lethal presentations of severe falciparum malaria and carries a high mortality rate, especially among the pediatric age group.

Epidemiology

According to the world malaria report issued by the WHO on 4th December 2019, there were nearly 228

million cases of malaria worldwide in 2018, along with an estimated 405,000 deaths from the disease.[2] The WHO African region (mainly Sub-Saharan Africa) still bears the largest burden of malaria morbidity, with 213 million cases (93%), followed by the WHO South-East Asia region (3.4%) and the WHO Eastern Mediterranean region (2.1%). More than half of the cases all over the world are accounted for by Nigeria (25%), the Democratic Republic of Congo (12%), Uganda (5%) and the rest of the Sub-Saharan African countries. Children under 5 years of age are the most vulnerable group affected by malaria, accounting for 272,000 (67%) of all malaria deaths worldwide in 2018.[2]

CM holds a special significance due to its predominance among young children and a high mortality rate even among treated patients. Out of the 85% of all deaths in 2018 occurring in the Sub-Saharan African region and India, the mortality due to cerebral malaria was about 10-20%. In endemic regions of Africa, children under the age of five years are mainly affected, while in South-East Asia it is observed mostly in young adults. Even though the mortality among patients of cerebral malaria has decreased via the use of effective anti-malarial drugs, it still remains high at 15% to 20%.[3,4] Without treatment, CM is almost always fatal, with about one-fourth surviving cases being afflicted by long term neurological sequelae including epilepsy, sensory and motor abnormalities, and cognitive impairment.[1,4]

CM is predominantly seen in low immunity populations such as children growing up in endemic areas, as compared to the adult population. It presents most commonly as seizures in young children, and may be associated with acute renal failure, acute pulmonary edema, and hepatic dysfunction in adults. It often presents as a multi-system disease and the prognosis depends heavily on the degree and severity of vital organ dysfunction.[5]

The parasite and the etiology of neurological manifestations in CM

There are five species of the *Plasmodium* parasite which can cause human illness, but *P. falciparum* is the one chiefly responsible for the severe neurological complications and high mortality rate among patients. The female *Anopheles* mosquito is responsible for the transmission of *P. falciparum* in humans, the parasite undergoing developmental stages in the liver and causing the disease manifestations via the erythrocytic cycle. The merozoites released by the liver invade the erythrocytes and release schizonts after passing through different morphological stages during a period of 48 hours inside the erythrocytes. The trophozoites and schizonts are usually sequestered within the deep vascular beds, but the ring stages can be clearly detected in the peripheral blood.[5]

A list of potential causes of neurological manifestations in cerebral malaria has been shown below in Table 1.[6-13]

Table 1: Causes of neurological manifestations in malaria.

Etiology	Comments
High grade fever	May lead to febrile convulsions and loss of consciousness
Anti-malarial drugs	Chloroquine may cause a transient neuropsychiatric syndrome, cerebellar dysfunction and acute intermittent porphyria can be seen in extremely rare cases; quinine and quinidine can lead to cinchonism (tinnitus and high-tone deafness); mefloquine has been seen to be associated with a central anticholinergic syndrome and in some cases, a self-limiting neuro-psychiatric reaction; artesunate treatment for falciparum malaria has also shown some adverse neurological effects such as slurring of speech, ataxia and seizures; neurological manifestations secondary to antimalarial drug treatment are characterized by the absence of high grade fever and of parasitemia on blood smears.
Hypoglycemia and hyponatremia	Hypoglycemia due to quinine therapy or as a manifestation of severe malaria, may present with impaired consciousness and seizures; hyponatremia due to repeated vomiting episodes, can also lead to altered sensorium.
Cerebellar involvement	May be seen in some cases secondary to hyperpyrexia induced damage to the Purkinje cells; uncommonly seen in adults and sequelae such as gait abnormalities and truncal ataxia may be seen in a small percentage of children; specifically associated with *P. falciparum* infection.
Psychiatric manifestations	May present as paranoid or manic syndromes in the acute stage; depression in late stages of the disease; other symptoms may include acute confusional state with transient amnesia, delirium with hallucinations and rarely features of schizophrenia; most symptoms are considered a sequelae of severe malarial encephalopathy.

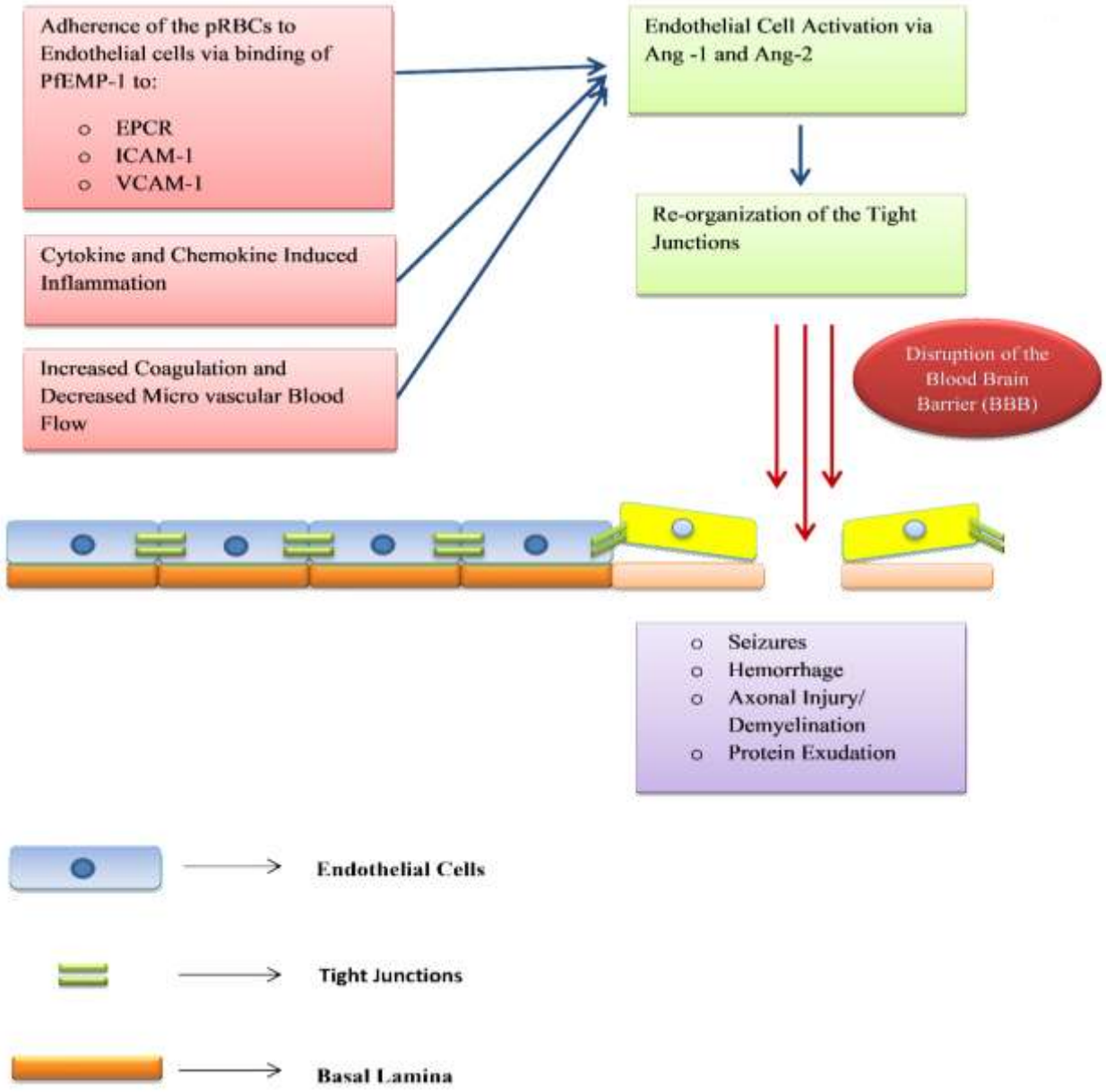

Figure 1: The pathogenesis of cerebral malaria.[14,15]

Mechanisms and pathogenesis of cerebral injury

The pathogenesis and the pathophysiology of CM has been described in Figure 1 and 2, respectively.[14-17]

Sequestration of the parasites in brain matter

The initial event is proposed to be the sequestration of *P. falciparum* parasites in cerebral microvasculature, which is mainly responsible for the pathogenesis and the resulting pathophysiological changes in the brain tissue around the sequestered parasites.[1] There is adherence of parasitized RBCs (pRBCs) to the endothelial lining via a group of parasite antigens, including *P. falciparum* erythrocyte membrane protein-1 (PfEMP-1). This PfEMP-1 mediates binding to host receptors of which, intercellular adhesion molecule-1 (ICAM-1) is the most important, it's expression being up regulated in areas containing the sequestered parasites.[1,14,15] The adherent erythrocytes agglutinate or use platelet mediated clumping to bind with other pRBCs and also form rosettes with non-parasitized erythrocytes. Sequestration impairs the ability of pRBCs to deform and pass through the cerebral microvasculature, resulting in decreased cerebral perfusion and aggravation of hypoxia leading to coma.[1,16,17]

Cytokine and chemokine mediated inflammation

The release of both pro-inflammatory and anti-inflammatory cytokines is triggered by the parasite antigens. The most important cytokine among these is the

tumor necrosis factor (TNF), which acts by up regulation of the ICAM-1 receptors on the cerebral vascular endothelium, thereby increasing cytoadhesion of the pRBCs.[18,19] Cytokine mediated synaptic modifications are also secondary to TNF mediated regulation, which might be responsible for the neurological syndrome of CM.[20]

Other cytokines and chemokines that are involved in the disease process are interleukin (IL)-1b, IL-6, IL-10 and NO, along with low levels of the chemokine RANTES (regulated upon activation, normal T cell expressed and presumably secreted).[21,22] Metabolites of the kynurenine pathway, quinolinic and kynurenic acid, may also play some role in the pathogenesis.

Endothelial injury and blood-brain barrier (BBB) disruption

Widespread endothelial activation is caused in vessels containing pRBCs due to cytoadherence to the endothelium, which leads to a significant increase in the circulating endothelial micro particles (EMPs).[23] In addition, further injury to endothelial cells is caused due to the clumping of pRBCs with platelets, through a direct cytotoxic effect.[15] Plasma levels of endothelial regulators, angiopoietin-1 (ang-1) and angiopoietin-2 (ang-2) are altered, which further increases endothelial activation.[24] Disruption of the BBB at the sites of sequestration further attracts the perivascular macrophages due to the leakage of plasma proteins into perivascular spaces.[25]

Intracranial hypertension could be caused by sequestration as well as increased cerebral blood flow from anemia and seizures. It reduces the cerebral perfusion pressure and nutrient and oxygen delivery, leading to brainstem herniation, global ischemic injury, and death.[25] This ischemic injury can be visualized on computerized tomography scans in which the pattern of injury is consistent with a significantly reduced perfusion pressure.[26]

Malarial encephalopathy and associated clinical features

CM presents as a diffuse encephalopathy with few focal neurological signs. The patient is febrile and unconscious, with a passive resistance to neck flexion which is mostly of a lesser degree than that associated with meningitis.[2,27] Impaired consciousness, which is considered to be the hallmark of CM, is thought to be secondary to parasite sequestration in the cerebral micro-circulation as well as to metabolic derangements, hypoglycemia and neuronal inflammation.[19] Some of the commonly seen systemic abnormalities reported among children include hyponatremia (>50%), hypoglycaemia (30%), severe anaemia (20-50%), jaundice (8%) and metabolic acidosis. Approximately 75-80% of African children with CM have shown evidence of increased intracranial pressure.[28]

Seizures are an extremely common presentation in children with CM, accounting for more than 80% cases who present with seizures on admission and more than 60% who have recurrent seizures during hospital stay.[1] They are usually seen to manifest within 24 hours of disease onset in children but can present in adults after 24-72 hours of symptom onset. Status epilepticus is also commonly observed in children admitted with seizures. Coma can develop suddenly in children, with seizures following a few days of fever. Signs of intracranial hypertension and retinal changes (macular changes, hemorrhages and papilledema) are commonly observed, along with signs of brainstem involvement such as abnormal pupil size and reaction, dysfunctional gaze and ocular movements or abnormal respiratory patterns such as Kussmaul's breathing. Complications such as shock, hypoglycemia, dyselectrolytemia, severe metabolic acidosis and repeated seizures in the setting of deep coma signify an extremely poor prognosis.[1]

CM commonly presents with multi-system involvement in adults. The presentation may include pyrexia with headaches and generalized body aches, ultimately culminating in delirium and a deep coma. Seizures are seen less commonly (15-20% cases) as compared to children.[1,3] This is usually complicated by anemia and jaundice, shock, renal failure, lactic acidosis, coagulation defects and hemoglobinuria. Respiratory difficulties may develop secondary to pulmonary edema and acute respiratory distress syndrome.[1] The dysfunctional coagulation may also lead to cortical cerebral infarcts or cerebral venous/dural sinus thrombosis. Sepsis is commonly seen in patients with shock, which is responsible for the majority of deaths due to acute kidney injury and multi-organ failure.[29]

On examination, the blood pressure is usually normal to low with a rapid pulse. The peripheries although initially seeming to be well perfused, may become cold and clammy due to shock. Hypoglycemia is usually seen in severe malaria, occurring more commonly in children with CM and is usually not associated with signs of hypoglycemia such as profuse sweating. These hypoglycemic episodes differ in the fact that the impaired consciousness does not improve even after correction of the plasma glucose levels.[5]

On direct ophthalmoscopy, retinal hemorrhages are found in about 15% of patients.[30] These are boat or flame shaped, usually spare the maculae and sometimes resemble Roth spots with a pale center. The characteristic retinopathy in CM, which includes retinal whitening with occasional cotton wool spots, orange or white vessel discoloration, hemorrhages/exudates and uncommonly papilledema has been reported in more than 60% of children. In adults however, hemorrhages are seen in only 10-15% cases, but typically without the other vascular changes as seen in children.[30] Papilledema is mostly seen in children and is rarely associated with sixth nerve

palsies. The pupillary reactions are usually normal and the range of eye movements are full, although the gaze is observed to be dysconjugate. Although corneal reflexes are usually present, they may be lost in very deep coma.[31] There is loss of superficial reflexes along with a bilateral extensor plantar response, and some hypertonic patients may elicit ankle and patellar clonus.[5]

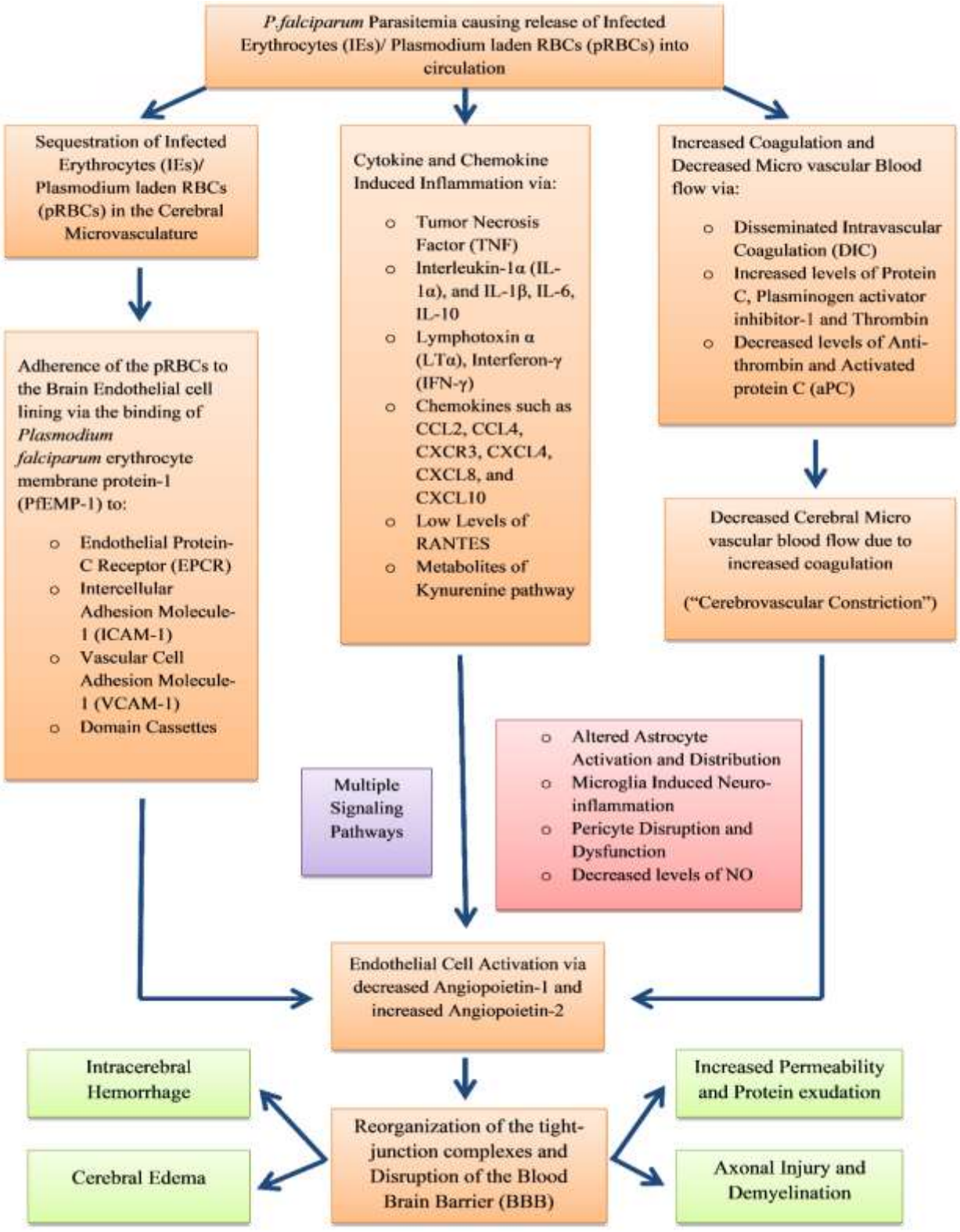

Figure 2: The pathophysiology and salient features of neuronal injury in cerebral malaria.[16,17]

In complicated cases, patients with severe malaria may develop disseminated intravascular coagulation (DIC), presenting as bleeding into the skin (petechiae/purpura) and from the upper gastrointestinal tract (hematemesis/melena).[2] Coexistent renal failure, electrolyte imbalance, severe jaundice, hypoglycemia and metabolic acidosis are the major factors responsible for the poor prognosis and outcomes in most patients. CM has a mortality rate of about 15-25% in children and 15-20% in adults, with some surviving patients developing neurocognitive impairments later in life due to the aftereffects of acute neuronal injury.[1,3,4]

Table 2: Neurological sequelae.[1,37-43]

Sequelae	Immediate	Long-term
Motor dysfunction	Spasticity (hemiplegia, quadriplegia); cranial nerve palsies; hypotonia	Spasticity (hemiplegia, quadriplegia); cranial nerve palsies
Movement disorders	Ataxia; tremors; dystonia	Dystonia
Visual defects	Blindness; mild visual impairment	Usually resolves
Speech impairments	Aphasia	Aphasia; defects in language, word finding, content, vocabulary and phonology
Defects in cognition and seizures	Impairments in working memory, attention and learning; generalized tonic-clonic seizures	Impairments in attention, executive function and working memory; generalized tonic-clonic seizures and secondarily generalized seizures
Behavioral deficits and neuropsychiatric complications	None	Attention difficulties, hyperactivity, conduct disorders, self-injurious behavior in children; post-malaria neurological syndrome (acute psychosis, hallucinations, catatonia) in adults

Seizures and other neurological sequelae

Seizures are a common feature of CM, the risk of seizures increasing with the increasing parasitic load.[32] On MRI scans, edema is seen signifying irreversible neuronal damage after prolonged and multiple episodes of seizures, which is replaced by gliosis over a period of time.[33,34] Factors proposed to be responsible for seizures in CM are downregulation of GABA receptors, sequestration of PRBCS in the brain, metabolic derangements, hypoglycemia and hyponatremia, and through the action of inflammatory mediators.

Some patients with coma secondary to seizures regain consciousness early and have a recovery without any neurological sequelae. Prolonged seizures can present with a status epilepticus like state which can prove lethal if complicated by aspiration and subsequent hypoxia. Seizure recurrence is prevented by the use of prophylactic anti-convulsants, but their use neither prevents the risk of subsequent epilepsy nor does it improve the neurocognitive outcome.[35,36] The prognosis and outcomes mainly depend on the duration of seizures and on the neuronal damage caused by the accompanying hypoglycemia and metabolic acidosis.[5] A specific class of patients presenting with a primary neurological syndrome associated with seizures without severe metabolic disturbances are often seen to have extremely poor neurocognitive outcomes. In these cases, intracranial hypertension is commonly observed and the coma persists for a time period well beyond after the resolution of seizures.[5]

The pathogenesis of the various neurological sequelae and their principal features have been described in Figure 3 and Table 2 respectively.[1,37-43]

Diagnosis

Microscopy of Giemsa-stained blood smears and the demonstration of the asexual forms of *P. falciparum* in peripheral blood remains the gold standard for confirmation of malaria diagnosis. In some cases, due to the sequestration of parasitized RBCs in cerebral circulation or prior treatment with antimalarial drugs, the asexual forms may not be seen in the peripheral blood smear. For such cases, a minimum of three smears six hours apart should be examined and malaria should be ruled out only if at least three smears turn out to be negative.[44] Confirmation of suspected cases can also be done by rapid diagnostic tests (RDTs) or repeat microscopy. However, treatment should be initiated promptly if the clinical presentation indicates severe malaria and there is no other alternative diagnosis.[45]

Malarial RDTs provide a quicker and a more practical solution at the level of community health workers (CHWs), who can be trained effectively in their use, without the requirement of any special equipment.

Parasites sequestered in the deep vascular compartments, which are normally undetectable by peripheral blood smear examination can also be detected by RDTs. They have a sensitivity of about 95-99% depending on parasite count and a high specificity of >99%. High-quality RDTs have now become the preferred option for many malaria control programs in tropical countries because of their simplicity and ability to provide early and accurate results.[46] The most commonly used are the histidine-rich protein II (HRP2) based RDTs for tropical areas where *P. falciparum* is the cause of majority of infections. HRP2 based RDTs can also better withstand the heat and temperature fluctuations of tropical countries, as compared to the enzyme based RDTs.[47,48]

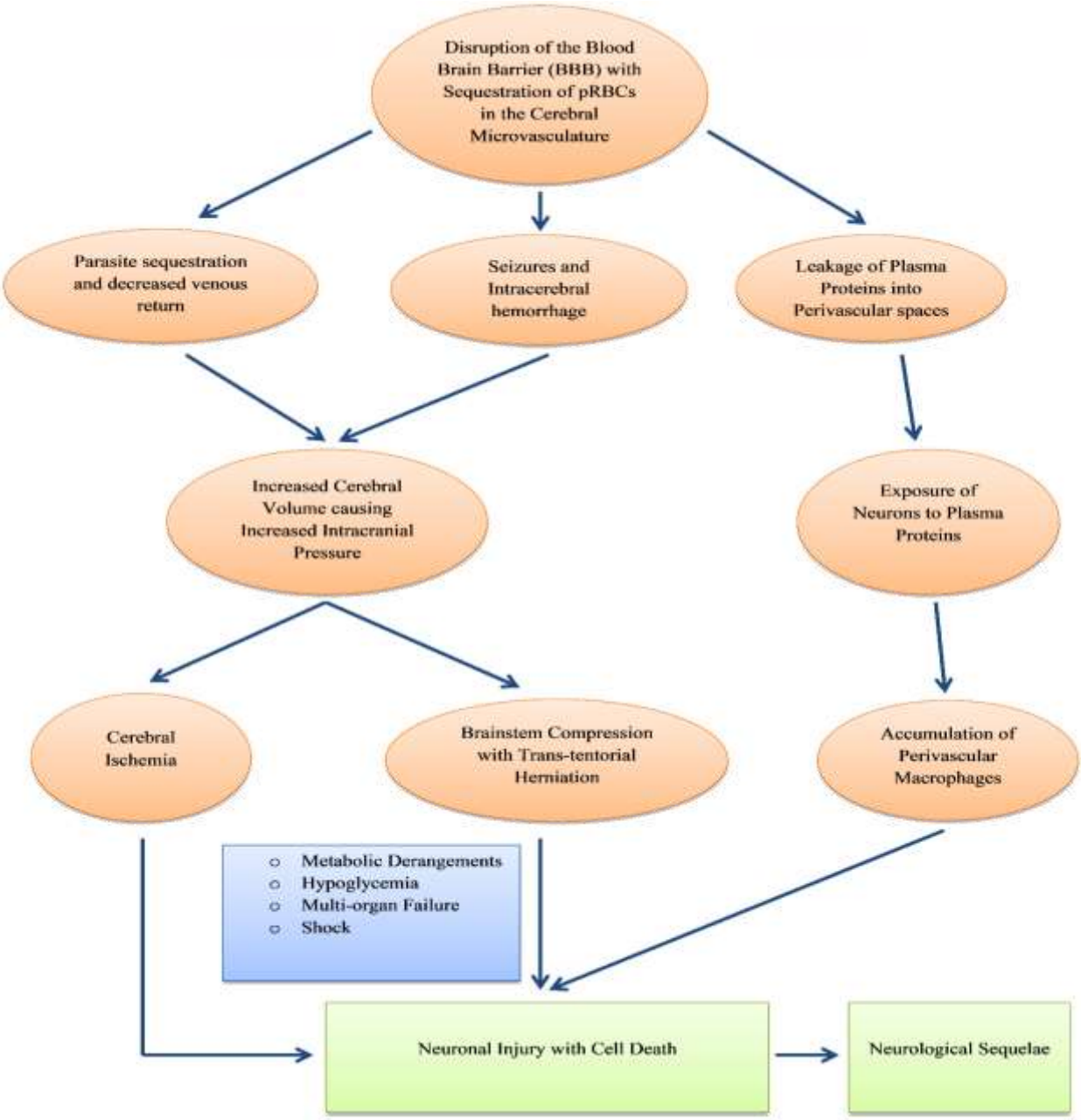

Figure 3: Mechanisms of neuronal injury and neurological sequelae in cerebral malaria.

CSF examination via lumbar puncture is necessary to exclude other causes of febrile encephalopathy. Lumbar puncture is not contraindicated in cases of CM and must be done as necessitated for diagnosis exclusion. CSF findings are generally normal in cerebral malaria, except a mild pleocytosis and rise in protein levels. EEG shows non-specific abnormalities such as spike wave discharges and a burst suppression pattern.[44]

CT scans are usually normal or might show edema and cortical/subcortical infarcts in some patients. However, some reported features include cerebral edema, thalamic

hypo-attenuation and cerebellar white matter hypo-attenuation from infarcts.[23] T2 Flair MRI may demonstrate non-specific hyper intensities located in the corpus callosum, bilateral periventricular white matter, and/or bilateral thalamic regions. Regions of hypointensity may be seen which represent either areas of hemorrhage in the infarcted tissue or petechial micro-bleeds.[49]

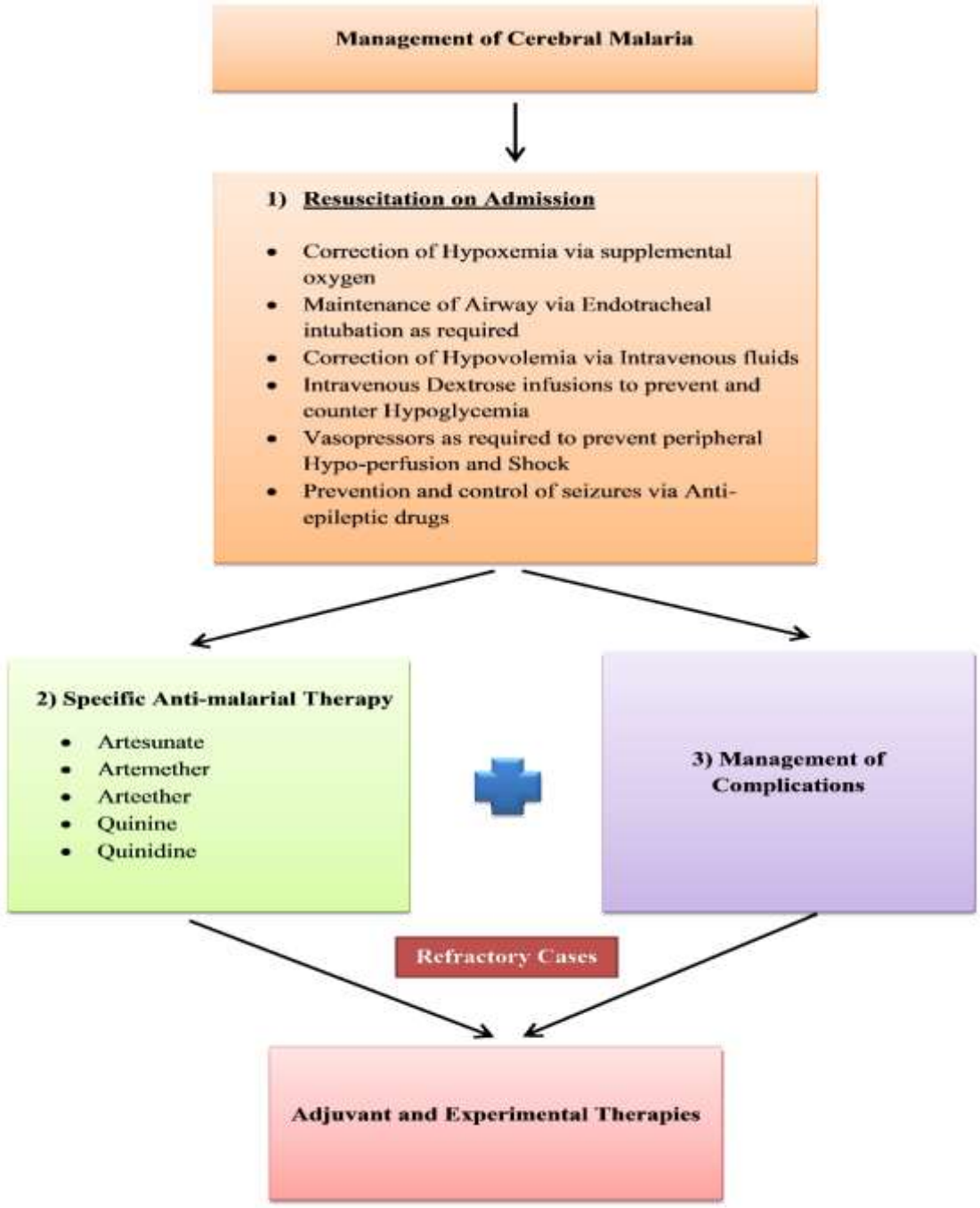

Figure 4: Treatment algorithm for cerebral malaria.

Treatment protocol for CM

The treatment of cerebral malaria should be started without waiting for the confirmation of diagnosis, especially in endemic areas. It includes initial resuscitation of the patient, specific antimalarial therapy, management of associated complications and newer and experimental adjuvant therapies.[14,50,51]

A concise treatment algorithm has been given in Figure 4.

Table 3: Complications of CM and their management.

Complications	Management
Shock	Intravenous fluid support; parenteral anti-malarials and antibiotics
Hypoglycemia	Continuous dextrose infusions; regular blood glucose monitoring
Seizures and coma	Maintenance of adequate airway; intravenous/rectal diazepam
Metabolic acidosis	Exclude hypoglycemia and septicemia; intravenous sodium bicarbonate to be used with extreme caution d/t risk of sodium overloading
Acute kidney injury	Exclude hypovolemia, septicemia and obstructive causes; dialysis support in severe cases
Anemia and hyperpyrexia	Red cell concentrate (RCC) transfusion as required; cold sponging and acetaminophen; avoid NSAIDs
Acute pulmonary edema	Head end elevation/ propped up positioning; oxygen supplementation; diuretics; restriction of fluids
Disseminated intravascular coagulation (DIC)	Fresh frozen plasma (FFP) transfusion; administration of vitamin K; treatment of sepsis via necessary antibiotics

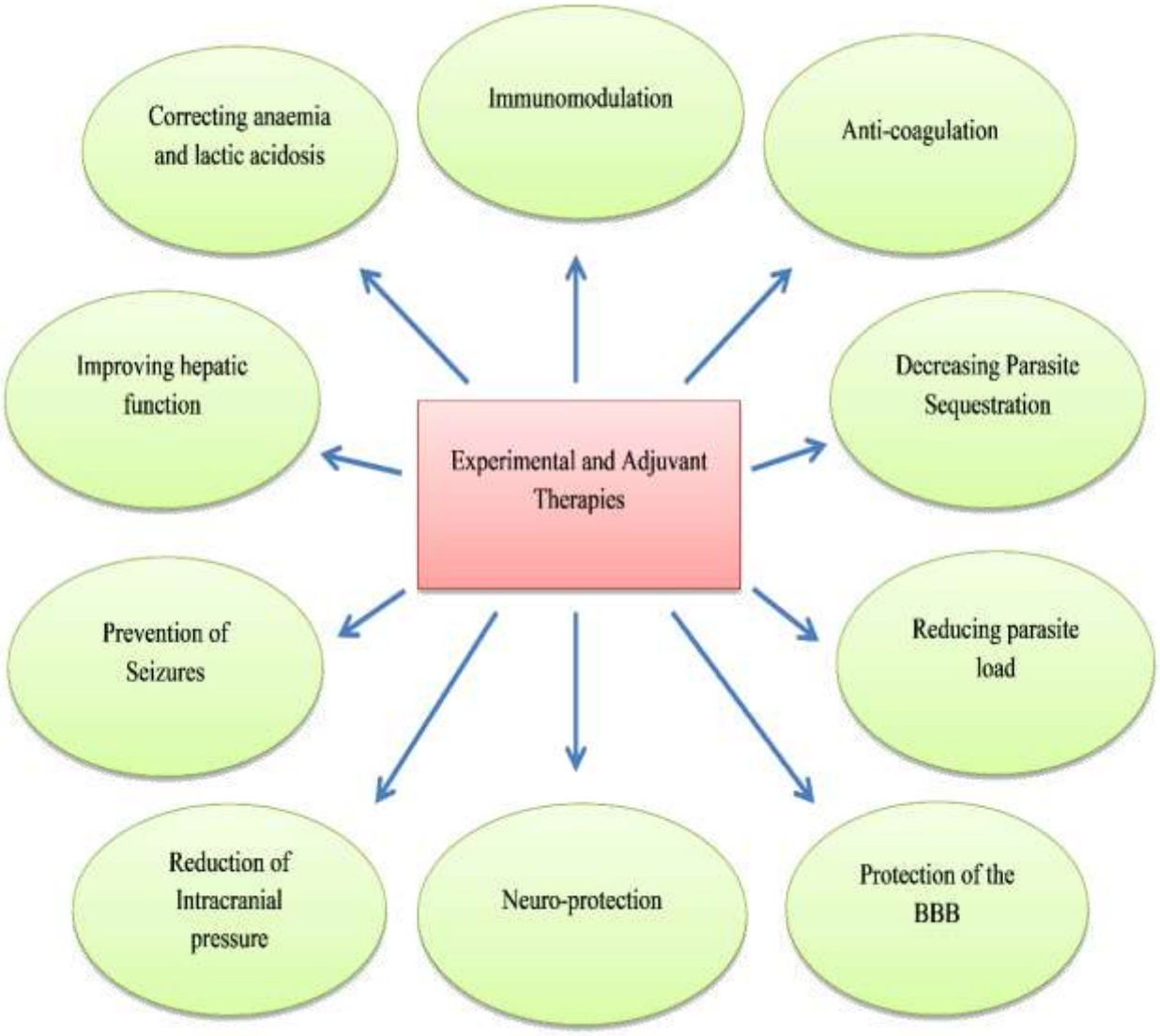

Figure 5: Recent and experimental therapies for CM.[58]

Table 4: Immune modulation therapies in CM.[1,58]

Immune modulation	Remarks
Anti-TNF therapy	No significant benefit in mortality rates, with an increased risk of neurological sequelae in the experimental group; pentoxifylline (PTX), a TNF-α inhibitor showed improvement in survival and coma recovery time in one study, but no clinical benefit in another recent study
Intravenous immunoglobulin	Higher mortality and frequent neurological sequelae in children; no clear benefit noted
Corticosteroids	No significant decrease in mortality rates with an increased risk of pneumonia and gastrointestinal bleeding in the experimental group; encapsulated β-methasone hemisuccinate (BMS) in liposomes found to be less toxic in mice than the unencapsulated drug, along with improved survival and prevention/retarding progression of the cerebral syndrome
Oral activated charcoal (oAC)	Acts through modification of the immune response against malaria infection, with a significant reduction in pro-inflammatory cytokine levels and improvement in survival; safe and well tolerated in humans in a phase I trial along with parenteral artesunate
Curdlan sulfate	Potent human immunodeficiency virus (HIV) entry inhibitor, with some anti-coagulant properties; inhibits *P. falciparum* in vitro, by certain direct and non-specific effect on cytoadhesion and resetting; safe and appeared to reduce the severity of the disease process, but no significant difference in mortality
PPAR-ɣ agonists	Act as neuro -protective agents by anti-inflammatory and anti-oxidant effect, along with a decrease in neurovascular permeability; rosiglitazone modulates host immune response to malaria by improving survival and reducing neurological impairments; safe and well tolerated, with lower levels of pro-inflammatory biomarkers, reduced endothelial activation and faster parasite clearance
Curcumin	Anti-inflammatory molecule that scavenges reactive oxygen and nitrogen species; additive anti-parasitic activity when used in combination with artemisinins
Nitric oxide (NO)	Low levels of NO can result in activation of the cerebral vascular endothelium as well the up regulation of the endothelial adhesion molecules (EPCR, ICAM-1 and VCAM-1); use of inhaled NO (iNO) was found safe but without significant benefit for the treatment of SM in children in two RCTs; intravenous administration of L-arginine to increase NO levels (and reduce ang-2 levels) or by increasing the cofactor bioavailability required for nitric oxide synthase (NOS) activity remain possible interventions
Antibody dependant mechanisms	Certain *P.falciparum* cytophilic antibody subclasses such as IgG1 and IgG3 have been seen to offer protection against severe malaria
Modulation of mTOR (mammalian target of rapamycin) protein	Rapamycin*:* drugs that inhibit the mTOR pathway have been shown to be anti-parasitic; treatment with mTOR inhibitor rapamycin protects against experimental CM in a mouse model when administered within the first 4 days of infection; action was mediated via protection of the blood brain barrier and preventing influx of both pRBSc and inflammatory cells into the brain. Leptin: appetite suppression hormone, but also activates adaptive immune and inflammatory responses; increased in levels of leptin observed upon infection in a mouse model of cerebral malaria, with the action mediated through activation of the mTOR protein through action on the cytotoxic T cells; reduction in leptin levels through any form of mediation would result in mTOR inhibition leading to increased survival
Co-infections	HIV: considerable evidence that HIV increases susceptibility to malaria[79-81] via a decrease in the levels of IL-10 mRNA and increase in the TNF-α levels; HIV co-infection was also associated with higher placental parasite load; hepatitis B- co-infected individuals presented with lower parasite load and decreased levels of pro-inflammatory cytokines, but findings not found to be significant. Helminth infections: increased rates of infection and parasitemia were observed in helminthic co-infections via reduced inflammatory signaling and

Continued.

Immune modulation	Remarks
	decreased rates of immune-mediated disease; this was attributed to the chronic activation of the CD23 receptor and decreased circulating levels of soluble CD23, along with increased expression of IL-10 and an increased expression of the Treg marker FoxP3 among those with helminthic infection. Schistosomiasis: co-infection is associated with increased risk of malaria infection and higher parasitemia in murine models, associated with elevated levels of IL-6, IL-4 and IFN-γ levels. Filaria: in malaria co-infection, filarial infection is postulated to modulate through interferon regulatory factor-1 signaling by CD4 cells and by suppression of IL-12 secretion from antigen presenting cells; in the murine cerebral malaria model using *P. berghei* ANKA, filiarial infection with *Litomosoide sigmodontis* was seen to be protective against the development of cerebral malaria.
Erythropoietin	Improvement in clinical signs seen in murine models; acts via reduction of neural hypoxia

Table 5: The various adjuvant treatment modalities for CM.[58-60]

Adjuvant therapy	Remarks
Decreasing cytoadherence and parasite sequestration	Levamisole, an anti-parasitic agent showed potential to decrease cerebral sequestration in vivo in *P.falciparum* infected cases; no significant benefit seen when administered along with intravenous artesunate
Seizure prevention	Seizures in malaria associated with a higher mortality and more frequent neurological sequelae; levetiracetam showed a better safety profile than phenobarbital and a similar effect in the control of neurological complications and mortality
Anticoagulant drugs	Sevuparin sodium given as an intravenous infusion in combination with atovaquone-proguanil, in adults with uncomplicated malaria led to reduced merozoite invasion and desequestration of plasmodium infected RBCs; safe and well tolerated but requires further research
Reducing parasitic density	Exchange blood transfusions (EBT) act via replenishment of uninfected and healthy erythrocytes in place of parasite laden RBCs; no significant improvement seen in parasite clearance or patient survival in artesunate-treated patients
Correcting anaemia and lactic acidosis	Correction of anaemia via erythropoietin; stimulation of pyruvate dehydrogenase activity via dichloroacetate (DCA), and subsequent removal of pyruvate, the lactate precursor
Improving hepatic function	Ursodeoxycholic acid (UDCA) was tested as an adjunctive therapy for improving hepatic function; safe but no significant improvement in hepatic function tests
Decreasing intracranial pressure	Although mannitol controlled intermediate intracranial hypertension and reduced cerebral edema, the duration of action and effect was not prolonged or sustained; no effect on mortality in children with CM was observed
Reducing oxidative damage	N-acetylcysteine (NAC) acts by scavenging free radicals and reducing the expression of endothelial ligands in malaria; no effect on mortality was observed with intravenously administered NAC in a controlled study

Initial resuscitation measures

As shown in the Figure 4, maintenance of an adequate airway is the initial and most important step for resuscitation. The patient is treated for hypoxia via supplemental oxygen and if needed, endotracheal intubation is done to prevent aspiration. The patient is screened for hypoglycemia and dextrose infusions are started as required. Hypovolemia needs to be corrected promptly via intravenous fluids as prevention of hypo-perfusion and shock is paramount. Episodes of seizures are treated with appropriate anti-convulsants (intravenous/rectal diazepam).[14]

Specific antimalarial treatment[50,51]

The drugs of choice for CM are parenteral artemisinin derivatives or quinine because of widespread resistance to chloroquine, intravenous route being preferred over intramuscular route. To prevent relapses via gametocyte transmission, a single 0.75 mg/kg (45 mg adult dose) primaquine dose should be given to all patients with

parasitologically-confirmed *P. falciparum* malaria. This dose is to be given on the first day of treatment in addition to ACT, except for patients with known G6PD deficiency, pregnant women and infants under 1 year of age.[51]

Artesunate

2.4 mg/kg body weight IV or IM given on admission, then at 12 and 24 hours, then once a day for a maximum of 7 days (dilution of artesunate powder required with 5% sodium bi-carbonate provided in the pack).

Quinine

20 mg salt/kg body weight on admission (IV infusion in 5% dextrose/dextrose saline over a period of 4 hours) followed by maintenance dose of 10 mg/kg body weight 8 hourly; infusion rate not exceeding 5 mg/kg body weight per hour; if parenteral quinine therapy needs to be continued beyond 48 hours, dose should be reduced to 7 mg/kg body weight 8 hourly; care should be taken to never administer bolus injection of quinine.

Artemether

3.2 mg/kg body weight IM given on admission then 1.6 mg/kg body weight per day.

Arteether

150 mg daily IM for 3 days in adults only (not recommended for children).

Parenteral treatment should be given for a minimum period of 24 hours once started. Once the patients can tolerate oral therapy or after at least 24 hours of parenteral therapy, they should get a full course of oral ACT. In special circumstances such as pregnancy, quinine should be used in the first trimester, whereas parenteral artemisinin derivatives are preferred in the second and third trimesters. The use of mefloquine along with ACT should be avoided in cerebral malaria due to the risk of neuro-psychiatric complications.

Primaquine is the only available drug which clears the circulating mature gametocytes that persist after ACT, thereby reducing the duration of gametocyte carriage.[52-54] It renders most patients free of gametocytes by day 14 after initiation of the ACT-primaquine regimen. WHO has recommended one dose of primaquine (0.75 mg/kg) in addition to ACTs for use in malaria elimination programmes as well as to stop the spread of artemisinin resistance. It is now recommended for use in first-line antimalarial treatment in many countries.[55,56]

Cerebral malaria due to Plasmodium vivax

Recently, a number of cases have been reported of cerebral malaria being caused by *P. vivax*. It should be treated like severe *P. falciparum* malaria, however, primaquine should be given for 14 days for preventing relapse as per guidelines, after the patient recovers from the acute illness. The currently recommended dose for this purpose is 0.25 mg base/kg/day (15 mg/day adult dose) for 14 days after parenteral artemisinin therapy.[51,57]

Management of Complications in CM

The various complications of cerebral malaria and their management have been described in Table 3.[14]

CONCLUSION

CM is a dreaded complication of *P. falciparum* infection. Early diagnosis is extremely important in such patients to prevent further complications and reduce impending mortality. Rapid diagnostic tests have come a long way in detection of the parasite and have immensely boosted the community defense against malaria. Prompt and rapid stabilization of the patient, adequate fluid supplementation and correction of electrolyte imbalance remain the most vital supplementary interventions in these cases, along with early induction of primary parenteral antimalarial therapy. Neurological sequelae including seizures are frequently observed in many treated and recovered cases, with some patients having to endure long term neurocognitive defects. Newer experimental and adjuvant therapies have been recently proposed, but most of them still require a lot of research and clinical trials to be effectively integrated into the treatment protocol for complicated cases of CM.

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