## Review Article

# Cerebral Malaria in Children: A Review of Pathophysiology, Clinical Manifestations and Management

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## ABSTRACT

Infection with malaria parasites may result in a wide variety of symptoms, ranging from absent or very mild symptoms to severe disease and even death. In general, malaria is a curable disease if diagnosed and treated promptly and correctly. Severe malaria occurs most often in persons who have no immunity to malaria or whose immunity has decreased.

Cerebral malaria (CM) collectively involves the clinical manifestations of Plasmodium falciparum malaria that induce changes in mental status and coma. It is an acute, widespread disease of the brain which is accompanied by fever. The mortality ratio is between 25 - 50%. If a person is not treated, CM is fatal in 24 - 72% hours. This article is meant to review the problem of cerebral malaria in children with respect to clinical features, pathophysiology and management.

Key words: cerebral malaria, children, pathogenesis, PfEMP-1 IFN-$\gamma$, TNF-$\alpha$

Malaria is the most important human parasitic disease. It is caused by an obligate intracellular protozoa Plasmodium falciparum, P. vivax, P. ovale and P. malariae. It is transmitted by female Anopheles mosquitoes, or may also transmitted via parenteral injection or congenitally. In malaria endemic areas, severe faciprum malaria usually develops after 6 months of age.1

Malaria is a public health problem in more than 90 countries. It affects about 5% of the world's population at any time and it is responsible for the death of more people than any other communicable disease except tuberculosis.2 It causes somewhere between 0.5 and 2.5 million deaths each year.3 More than 90% of all malaria cases are in sub-Saharan Africa. Young African children mainly succumb to death, especially in remote rural areas with poor access to health services.4

Malaria neurological complication, 'cerebral malaria (CM)' is arguably one of the most common non-traumatic encephalopathies in the world and remains a major cause of morbidity. It accounts for one in five of all childhood deaths in Africa. Although malaria occurs in millions of people, only 20 - 50% of the cases develop cerebral malaria. In-spite of the best possible care and intensive therapy with ancillary support, the mortality from cerebral malaria remains unacceptably high. In some reports CM accounts for up to 10% of all cases of P. falciparum malaria in hospitalized persons and for 80% of fatal cases. If a person is not treated, CM is fatal in 24 - 72% hours.

Like most countries in sub-Saharan Africa, Sudan carries a heavy malaria disease burden. It ranks high as the one of the most endemic country of the world. It accounts for 50% of malaria cases in the Eastern Mediterranean Region. It is estimated that more than 8 million cases and about 35,000 deaths occur per year. The disease accounts for 20% of all hospital deaths and the malaria case fatality rate for paediatric hospitals ranges between «515- per cent».5

The epidemiological pattern of severe malaria varies considerably from that of hyperdynamic regions in sub-Saharan Africa and there is considerable variation between the individual complications of severe malaria.6

**Severe Malaria**

Severe malaria occurs when P. falciparum infections are complicated by serious organ failures or abnormalities. It is usually manifests in African children growing up in malarious endemic areas.7

Many factors thought to contribute to P. falciparum virulence these include:-

a- The Redundancy and multiplicative Capacity of P. falciparum

P. falciparum is able to infect the entire polymorphic human population; this is due to variant surface antigens such as Plasmodium falciparum erythrocyte membrane protein-1 (PfEMP1) which specifically binds to adhesion molecule CD36 and thrombospondin which assists the parasite adherence to various receptors and removal from the circulation avoiding the splenic clearance.8

b- Parasitized RBCs Membrane Modification: These includefor mation of knob-like structures composed of proteins (PfEMP-1), protruding from their surfaces increasing cell wall rigidity and altering the metabolites transport. 9

c- Cyto-adherence and sequestration of parasitized erythrocytes. This is a specific interaction between RBCs and the vascular endothelium leading to sequestration of parasitized RBCs in deep organs predominantly in the brain, heart, lungs and sub-mucosa of the small intestine.10

d- Rosetting and Agglutination;

e- RBC Deformability: In severe malaria both parasitized (PRBCs) and non-parasitized RBCs (NPRBCs) become rigid due to oxidative damage to the RBCs comprising their flow through capillaries. This has strong predictive value for fatal outcome.11

The polymorphism of genes coding four human adhesion molecules; intercellular adhesion molecule-1 (ICAM-1), endothelial selectin (E-selection), CD36 are important variable in the susceptibility to severe malaria.12

The manifestations of severe malaria include among others; cerebral malaria with abnormal behaviour, impairment of consciousness, seizures, coma or other neurologic abnormalities and metabolic acidosis presenting as respiratory distress or severe anaemia. Compared with adults, children have a higher incidence of seizures.12The incidence and pattern of neurological complications are different and the patients often die with features of brain death. African children rarely develop renal failure or pulmonary oedema.13

**Cerebral malaria (CM)**

There is a clear need for a strict definition of cerebral malaria in order to properly diagnose and assess the condition. The term «cerebral malaria» often been loosely used in the medical literature to describe any disturbance of the CNS in a malaria infection. CM collectively involves the clinical manifestations of P. falciparum malaria that induces changes in mental status and coma.13, CM hence, is an acute widespread disease of the brain which is accompanied by fever.

In older children CM can be defined as in adults.

The Blantyre Coma Scale, a related diagnostic tool, has been used for young children 10 years of age or less.14,15 It was devised to assess young children responses (Table 1). However, there is considerable disagreement between observers in assessing the scale and the scale does not address the inability of

| Table: 1 Blantyre and Glasgow Coma Scales. | |
| --- | --- |
| **Blantyre coma Scale** *(Molynux et al. 1989)* | **Galsgow Coma scale** *(Teasdale & Jennett, 1974)* |
| Verbal | |
| 2. Appropriate cry | 5. Able to give name and age |
| 1. Inappropriate cry or moan | 4. Recognizable and relevant words |
| o. No cry vocalization. | 3. Incomprehensible, but complex |
| | 2. Cry or grunt |
| | 1. No response |
| Motor | |
| 2. Localizes pain. | 6. Obeys commands |
| 1. Withdrawal from pain | 5. Localizes pain. |
| 0. Non-specific or no response to pain | 4. Withdrawal from pain. |
| | 3. Flexes to pain |
| | 2. Extends to pain. |
| | 1. No response. |
| Eye | |
| 1. Directed eye movements | 4. Spontaneous eye opening |
| 0. Not directed | 3. Opens eyes to voice |
| | 2. Opens eyes to pain |
| | 1. No eye opening |

with severe malaria and a summated score of 2 is used to define cerebral malaria in many studies.15 The Blantyre coma scale has similar components to the Glasgow coma scale but it measures different young infants to localize a painful stimulus.16

A Glasgow coma scale less than 8 has been proposed as part of the definition of CM.16A practical definition based on the Glasgow Coma Score exists.17 Its key elements are;

(1) Unrousable coma- No localizing response to pain persisting for more than six hours if the patient has experienced a generalized convulsion.

(2) Asexual forms of P. falciparum found in blood and

(2) Exclusion of othercauses of encephalopathy, i.e. viral or bacterial.

**Pathophysiology of Cerebral Malaria**

Cerebral malaria causes and pathophysiology is not well identified. To investigate the pathogenesis of CM, several animal models have been established in which animals are infected with parasitized RBCs by various types of Plasmodium. Although these animal models do not exactly reproduce the human disease, they nevertheless exhibit some similarities to human CM such as clinical signs of nervous system dysfunction and cerebral pathology.18

Infected RBCs become structurally and antigenically modified as a consequence of intracellular parasite development. Parasite encoded proteins such as histidine-rich proteins-1 give rise to RBC surface antigen.19These proteins link to cells surface produce knobby protrusions. The occurrence and severity of these early changes in the microcirculation correlated with the subsequent development of cerebral symptoms.20,21

The histopathological hallmark of malaria encephalopathy is the sequestration of cerebral capillaries and venules with parasitized red blood cells and non-PRBCs.22

Monocyte margination appeared to be the most significant factor associated with the development of cerebral symptoms. Ring-like lesions in the brain are major characteristics. The leukocyte sequestration in human CM at least in paediatric patients is now well substantiated, this agrees with murine CM animal models.23

Currently, there are two major hypotheses explaining CM aetiology, these are the mechanical and the humoral hypotheses.24

i- The mechanical hypothesis: The underlying defect seems to be blocking of the cerebral microcirculations by the parasitized RBCs. These cells develop knobs on their surface increasing their cytoadherence properties as a result; they tend to adhere to the endothelium of capillaries and venules.25This leads to sequestration of the parasites in the deeper blood vessels.

The mechanical hypothesis asserts that a specific interaction between a P. falciparum PfEMP-1 and ligands on endothelial cells, such as ICAM-1 or E-selectin, reduces microvascular blood flow and induces hypoxia.26 Sequestration of P. falciparum infected erythrocytes in post-capillary brain endothelium is induced by immune response on vascular receptors such as CD36. The degree of binding to CD36 is correlated with biochemical indicators of disease severity. Other receptors such as intracellular adhesion molecule-1 (1CAM-1), E-selectin and inducible nitric oxide synthase (iNOS) significantly reduce the RBCs cytoadherence with increased expression in the cerebral vessels of patients with cerebral malaria.27

Rosetting is associated with severe malaria in African children.28 Rosetting of the parasitized and non-parasitized red cells and decreased deformability of the infected red cells further increases the obstruction of the microcirculation. It has been observed that the adhesiveness is greater with the mature parasites. Rosetting thus, accounts very well for CM histopathological hallmark and its characteristic coma condition. However, this hypothesis is inadequate to explain the relative absence of neurological deficit even after days of coma.28

Petechial haemorrhage into the brain indicates that, brain vasculature in patients with P. falciparum malaria is often damaged. Several studies using dye extrusion into tissue have documented that vascular permeability is markedly increased in the brain.29

However, the exact contribution of vascular leakage to human CM is still not defined and no significant vascular leakage was detected into brains of patients with severe P. falciparum malaria.30

No definite evidence of cerebral oedema has been found on imaging studies. 80% children with CM have raised intracranial pressure due to increased cerebral blood volume and biomass rather than increased permeability.

Animal models in susceptible mice infected with P. berghei develop neurological abnormalities 6 days after injection with parasite.31These mice exhibit brain edema, petechial haemorrhages and monocyte infiltration. In addition, injection of P. berghei-infected mice with folic acid results in convulsions, indicating that folic acid has crossed the normally impermeable blood-brain barrier and is mediating altered brain signaling.32

ii- The humoral hypothesis: This hypothesis suggests that a malarial toxin may be released that stimulates macrophages to release tumor necrosis factor TNF-$\alpha$ and other cytokines such as IL-1.33 The cytokines themselves are not harmful but they may induce additional and uncontrolled production of nitric oxide. Nitric oxide would diffuse through the blood-brain barrier and impose similar changes on synaptic function as do general anesthetics and high concentrations of ethanol leading to a state of reduced consciousness. The biochemical nature of this interaction would explain the reversibility of coma.34

Tumor necrosis factor and gamma interferon (IFN- $\gamma$) were shown to be important mediators in the pathogenesis of CM. Second, helper T lymphocytes play a significant role in the development of murine CM.23

**The role of IFN-$\gamma$ and its receptor in CM**

Gamma interferon IFN-$\gamma$ is produced in abundance during clinical episodes of malaria.35 The role of IFN-$\gamma$ in the pathology of malaria

disease was demonstrated by murine model of CM in which disruption of interferon gamma receptor 1 gene (IFNGR 1) was protective against cerebral complications of P. berghei.36

Pathogenic Role of TNFR2

Previous results suggested that TNF is a key element in the pathogenesis of experimental CM. High levels of this cytokine is noticed in the serum at the time of CM. More recently, additional confirmation of the pathogenic role of TNF in CM has been provided in experiments with transgenic mice expressing high levels of TNF receptor 1 (TNFR1).37 The interaction between membrane TNF and TNFR2 is crucial to the development of the neurological syndrome seen in severe malaria.38 More recently, TNFR2 was shown to be important in endothelial cell apoptosis in the absence of sensitizing agents, i.e., under pathophysiologically relevant condition.39

The receptor involved in the parasite-induced monocyte and macrophage stimulation has not been characterized. Malaria toxins are important molecules that are responsible for the direct induction by the parasite of TNF secretion by host monocytes.40

Platelet-Endothelial Interactions in Microvascular Pathology beyond Cerebral Malaria: The effects of anti-LFA-1 monoclonal antibody (anti-LFA-1MAb) on CM and on platelet accumulation in brain vessels may offer insight into the mechanism of action of this antibody in vivo. Apart from their beneficial role in haemostasis, platelets also in vitro experiments with human cells have indicated a role for LFA-1 in platelet-endothelium interactions, substantiated the fusion phenomenon and confirmed that platelets can potentiate the TNF-induced endothelial killing. A pathogenic role for platelets is also suspected in disorders other than CM, such as gram-negative bacterial septic shock, acute respiratory distress syndrome, vasculitides pulmonary fibrosis, tumor

metastasis, transplant rejection, stroke, brain hypoxia and related conditions. Indeed, platelets have been detected during rejection episodes41

**Involvement of Cell Adhesion Molecules**

Tumor necrosis factor can induce or upregulate various cell adhesion molecules(CAM) on endothelial cells; the expression of these molecules was analyzed by immunohistochemistry. Brain vessels from mice with CM showed a marked upregulation of ICAM-1 and vascular cell adhesion molecule 1(VCAM-1).42An attempt to prevent CM by intravenous injection of anti-TNF monoclonal antibodies(MAbs) directed against LFA-1, Mac-1, ICAM-1, VCAM-1, VLA-4 and P-selectin; showed that only anti-LFA-1 MAb proved to be efficient. The important role of ICAM-1 was confirmed using a SCID mouse model in which P. falciparum-infected human RBC adhere to brain ICAM-1 and more recently using ICAM-1-deficient mice.43

An adhesion molecule CD36 also known as platelet glycoprotein IV or IIIb, is an 88 kDa membrane protein expressed on the surface as multi-ligand receptor of a wide variety of cell types such as platelets, endothelial cells, monocytes and macrophages. It is involved in host defense against P. falciparum. CD36 is commonly deficient, particularly in certain ethnic groups including Africans. Its role in CM is debatable.44

Obstruction to the cerebral microcirculation results in hypoxia and increased lactate production due to anaerobic glycolysis. The parasitic glycolysis may also contribute to lactate production. In patients with CM, C.S.F. lactate levels are high and significantly higher in fatal cases than in survivors. The adherent erythrocytes may also interfere with gas and substrate exchange throughout the brain. However, complete obstruction to blood flow is unlikely, since the survivors rarely have any permanent neurological deficit.

The mechanism of coma is not clearly known.

Increased cerebral anaerobic glycolysis, interference with neurotransmission by sequestered and highly metabolically active parasites has been blamed. Cytokines induce a potent inhibitor of neurotransmission, nitric oxide (NO), synthesis in leukocytes, smooth muscle cells, microglia and endothelium.

**Clinical Manifestations**

Cerebral malaria is an acute widespread disease of the brain which is accompanied by fever. In severe P. falciparum malaria the neurological dysfunction can manifest suddenly following a generalized seizure or gradually over a period of hours.46The clinical manifestations however, are numerous but there are three primary symptoms generally common to both adults and children:

(1) Impaired consciousness with non-specific fever,

(2) Generalized convulsions and neurological sequelae and,

(3) Coma that persists for24 -72% hours, initially arousable and then unarousable.

**Neurological Signs in Cerebral Malaria:**

Mild neck stiffness may be seen, however, neck rigidity and photophobia and signs of raised intracranial pressure are absent. Retinal haemorrhages occur in about 15% of cases, exudates are rare. Pupils are normal. Papilloedema is rare and should suggest other possibilities. A variety of transient abnormalities of eye movements, especially dysconjugate gaze are observed. Fixed jaw closure and tooth grinding (bruxism) are common. Pouting or showing displeasure may occur or may be elicitable, but other primitive reflexes are usually absent. The corneal reflexes are preserved except in a case of deep coma. Motor abnormalities like decerebrate rigidity, decorticate rigidity and opisthotonus can occur. Deep jerks and plantar reflexes are variable. Abdominal and cremasteric reflexes can not be elicited. These signs help in distinguishing CM from behavioural problems due to fever of other causes. Rarely, cases

of falciparum malaria may present with cerebellar ataxia with unimpaired consciousness. It may even occur 34- weeks after an attack of falciparum malaria. It completely recovers over 12- weeks.6

**Management of Cerebral Malaria in Children**

Severe malaria is a medical emergency and may rapidly progress to death without prompt and appropriate treatment. The main objective of the treatment of severe malaria is to prevent the patient from dying; prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities are secondary objectives.

Light microscopy of well stained thick and thin films by a skilled microscopist has remained the «gold standard» for malaria diagnosis. However, microscopy cannot detect parasite sequestered deep in the vascular compartment and in case of mixed infection often one species suppresses the other, thereby making detection of the suppressed one difficult.46 Blood gases and acid base deficit, renal function profile and blood glucose are useful predictors of the outcome

Cerebrospinal fluid analysis may have to be done in all doubtful cases and to rule out associated meningitis. In malaria, C.S.F. pressure is normally elevated, fluid is clear and WBCs are fewer than 10/ $\mu$l; protein and lactic acid levels are elevated.47

Electroencephalogram may show non-specific abnormalities and C.T. scan of the brain is usually normal.48 In addition to brain swelling, cortical infarcts and white matter lesions can be seen on MR examinations obtained during the course of cerebral malaria. White matter lesions can regress with effective treatment. The MR pattern is compatible with toxicity leading to intravascular engorgement and oedema and in some cases, to irreversible myelin damage.49

Meticulous nursing is the most important aspect of management in patients with CM and coma. A clear airway must be maintained. In cases of prolonged deep coma, endotracheal intubation may be indicated. Naso-gastric aspiration is important to prevent aspiration pneumonia. Urethral catheter has to be inserted for monitoring urine output in any comatose patient. All children with cerebral malaria should be admitted to an ICU if possible and children with impending respiratory failure should be placed on ventilatory support.

It is quite helpful to maintain strict intake/output records and to monitor the vital signs every 46-hours.50 Observe for high coloured or black urine. Changes in levels of sensorium, occurrence of convulsions should also be observed.

It is crucial to control or prevent seizures as they can cause neuronal damage and are associated with a fatal outcome. Witnessed seizures are managed with slow diazepam (0.2 mg/kg IV maximum of 10 mg or 0.4 mg/kg per rectum) or paraldehyde (0.1 mL/kg IM). Because diazepam can worsen respiratory depression, the patient's respiratory status should be monitored carefully after diazepam administration. Patients with recurrent seizures should be treated with Phenobarbital or Phenytoin, as one would treat a patient with status epilepticus. Phenobarbital prophylaxis for seizures is not recommended in children with cerebral malaria. Large studies in African children demonstrated a higher mortality rate in children who received Phenobarbital prophylaxis compared to controls.51

Hypoglycemia is common in children below 3 years of age especially with hyperparasitemia or with convulsion. It also occurs in patients treated with quinine. Manifestations are similar to those of cerebral malaria so it can be easily overlooked. Blood sugar should be Monitored every 4 to 6 hours.

Exchange transfusion generally only been justified when peripheral parasitaemia exceeds 10% of circulating erythrocytes. The role of these blood

transfusions remains highly controversial, as they are both expensive and potentially dangerous in many malaria-endemic areas.

Pentoxifylline helps microcirculatory flow by reducing the red cell deformability and blood viscosity, decreases systemic vascular resistance and impairs platelet aggregation thus improving microcirculatory flow.

Desferrioxamine this is an iron-chelating adjuvant agent with antimalarial properties is suggested as it reduces the formation of reactive oxygen species by reducing amount of free iron.52

The following drugs should not be administered: Anti-Inflammatories such as corticosteroids. However, there have been few controlled studies demonstrating benefit. other antiinflammatory drugs; low molecular weight dextran; adrenaline; heparin; hyperbaric oxygen; cyclosporin should be avoided.

Dehydration and hypovolemia in children with cerebral malaria should be corrected with intravenous fluids or colloid. Lactic acidosis can be corrected by aggressive management of malarial infection, volume replacement if the patient is dehydrated and transfusion of blood as appropriate.

The mortality of untreated severe malaria can be 100%, but with antimalarial treatment, the overall mortality falls to 15–20%. As death from severe malaria can occur within hours of admission to hospital or clinic, it is essential that therapeutic concentrations of antimalarial are achieved as soon as possible with intravenous antimalarials. Further, gastrointestinal intolerance and erratic intestinal absorption make the oral route of administration unreliable in these patients. As resistance to antimalarial drugs can complicate matters further, proper choice of antimalarials to start the treatment is of utmost importance; changing the drugs or adding of drugs half-way through the treatment only

complicates the issue and adds to the adverse effects of treatment. Children with cerebral malaria should be treated with intravenous or intramuscular Quinine, or intramuscular Artemisinin derivatives.53

Consequences and Prognosis of Cerebral Malaria

Cerebral malaria carries a mortality of around 20% in adults and 15% in children. Factors associated with a fatal outcome included deep breathing or acidosis (base excess below -8), hypotension (systolic blood pressure < 80mmHg), raised plasma creatnine (>80 $\mu$mol/l), low oxygen saturation (<90%), dehydration and hypoglycaemia (<2.5 mmol/l). Approximately 7% of children who survive CM are left with permanent neurological problems. These include weakness, spasticity, blindness, speech problems and epilepsy. Recent evidence suggests that some children who appear to have made a complete neurological recovery from cerebral malaria may develop significant cognitive problems (attention deficits, difficulty with planning and initiating tasks, speech and language problems), which can adversely affect school performance and persist for years after the attack.54 The limited availability of specialized care for such children indicates that opportunities for subsequent learning and for attainment of independence, are compromised even further.

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