



Cerebral Malaria

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Abstract

Cerebral Malaria (CM) is the most severe neurological presentation of acute falciparum malaria, the clinical hallmark of which is the presence of coma. It is a diffuse encephalopathy associated with seizures in at least 80%, and status epilepticus, in up to a third of cases. The case fatality rate of CM ranges between 5% and 50%. Although most survivors make a full recovery, neurological sequelae such as hemiplegia, speech problems, cortical blindness and epilepsy occur in 3-31%. *Plasmodium falciparum* is responsible for almost all the mortality from malaria and is the only species that appear to directly affect the central nervous system causing neurological deficits and cognitive sequelae. The World Health Organization estimated that more than 83% of *P. falciparum* malaria occurs in sub-Saharan Africa where children bear the brunt of the disease with over one million children dying annually. The aim of this review is to provide an update on cerebral malaria.

Keywords: Cerebral malaria; Update; Sequelae

Introduction

Malaria is probably one of the oldest diseases known to man for millennia. It is an infectious disease caused by the parasite called *Plasmodia*. Five species of plasmodium cause malaria in man, namely, *Plasmodium vivax* (*P. vivax*), *Plasmodium falciparum* (*P. falciparum*), *Plasmodium ovale* (*P. ovale*) *Plasmodium malariae* (*P. malariae*) and *Plasmodium knowlesi* (*P. knowlesi*) [1,2].

Plasmodium falciparum is responsible for almost all the mortality from malaria and is the only species that appear to directly affect the central nervous system causing neurological deficits and cognitive sequelae [1,3,4].

Malaria seems to have been known in China for almost 5,000 years. The *Nei Ching* (The Canon of Medicine) from 4,700 years ago apparently refers to repeated paroxysmal fevers associated with enlarged spleens and a tendency to epidemic occurrence [1] throughout history, a connection between swamps and fever was recognized. It was commonly assumed that malaria was contacted by breathing "bad air". Malaria was often part of ups and downs of nations; of wars and of upheavals. The disease supposedly had its origin in the jungle of Africa, where it is still very rampant. Man and malaria appear to have developed together over the years [5].

Epidemiology

About 60% of the cases of malaria worldwide, 75% of global *falciparum* malaria cases and more than 90% of malaria deaths occur in Africa south of the Sahara [6]. Malaria, distributed throughout the tropics and subtropics, is one of the most prevalent human infections worldwide. The distribution of malaria at present is considerably less than it was in the mid-1950s (140 countries or territories). At the end of the year 2004, 107 countries and territories had areas at risk of malaria transmission [6]. About 40% of the global population live in areas where there is risk of malaria transmission, 7% reside in areas

where malaria has never been under meaningful control, and 29% live in areas where malaria was once transmitted at low levels or not at all, but where significant transmission has been re-established. An estimated 350–500 million clinical malaria episodes occur annually; most of these are caused by infection with *P. falciparum* and *P. vivax* [1]. *Falciparum* malaria causes more than 1 million deaths each year [6]. It also indirectly contributes significantly to many other deaths, mainly in young children, through synergy with other infections and illnesses.

The patterns of malaria transmission and disease vary markedly between regions and even within individual countries [7,8] Malaria transmission may be endemic, epidemic or sporadic [9] Malaria can, in certain epidemiological circumstances, be a devastating disease with high morbidity and mortality, demanding a rapid, comprehensive response. In other settings, it can be a more pernicious public health threat. This diversity results from variations between malaria parasites and mosquito vectors, ecological conditions that affect malaria transmission and socioeconomic factors, such as poverty and access to effective health care and prevention services [1]. When *P. falciparum* is involved, malaria epidemics can be among the most lethal forces of nature unlike in endemic malaria where there is constant incidence of malaria over a period of many successive years in a given population [1,9,10].

Pathogenesis of Cerebral Malaria

Pathology

The hallmark (though not the pathognomonic) histopathological feature of cerebral malaria is engorgement of cerebral capillaries and venules with parasitized and non-parasitized red blood cells [11]. The parasitized red blood cells are confined to the microvasculature with little, if any, penetration of the brain parenchyma. The endothelium is microscopically intact [11], but immunochemical studies suggests that the blood-brain barrier may be impaired [12]. The brain is slightly swollen and the cut brain is often slate grey, with petechial

haemorrhages scattered throughout the white matter; hemorrhages are unusual in the grey matter [13]. Large haemorrhages, infarcts, and herniation's are rare. Large amount of intra - and extra - erythrocytic pigments are also seen. There is no evidence of thrombosis or vasculitis. Accumulation of glial cells surrounding hemorrhagic foci in white matter is called Durck's granuloma [10,14].

Pathophysiology

The pathophysiology of CM is not exactly known, but the following are some of the proposed hypotheses:

Permeability hypothesis (Maegraith and Fletcher)

It suggests that a toxic substance released by the parasites increases the permeability of the blood brain barrier (BBB) resulting in cerebral edema, coma, and death. This hypothesis is less favored because most adults with cerebral malaria have normal CSF pressure and blood brain barrier shows normal permeability to albumin and there is no response to corticosteroid therapy [15,16]. Imaging studies reveal that most adults with cerebral malaria have no evidence of cerebral edema [17,18]. In contrast, cerebral edema is more frequent in African children, although not a consistent finding [19]. Similarly, opening pressure on lumbar puncture in adult patients is usually normal but elevated in 78% children with cerebral malaria [20,21].

Toxic/ cytokine hypothesis

A glycolipid material similar to bacterial endotoxin (not a toxin in the strict sense) is released on merozoite rupture. This product called glycosylphosphatidylinositol, induces cytokine cascade from macrophage monocyte series and possibly endothelium, initially IL-1 and TNF alpha which then in turn induces IL-6, and IL-8. These are responsible for many of the signs and symptoms including paroxysms [14,22]. There is positive correlation between cytokine levels and prognosis. TNF alpha concentrations greater than 98 pg/ml of serum in patients with falciparum malaria is highly associated with disease severity, including coma, hypoglycemia, hyperparasitaemia and death [23,24].

Mechanical hypothesis

Apparent obstruction to the blood flow in the brain caused by parasitized erythrocytes might be the cause of coma and death in cerebral malaria [14]. A central feature is the inhomogeneous obstruction of the cerebral microcirculation by sequestered parasitized erythrocytes causing dysoxia but no infarction of brain tissue, and resulting in net lactate production by the brain [25]. Reduced red cell deformability and other factors related to rosetting and auto agglutination contribute to the compromised microcirculation. This does not exclude involvement of other host or parasite derived factors in the pathogenesis of coma; in fact impaired blood flow might focus these. Local overproduction of nitric oxide or yet to be evaluated other cytokines might impair neurotransmission, but their roles remain hypothetical [26].

The Processes Involved in The Pathophysiology of Cerebral Malaria are

Sequestration

This is central to pathophysiology of falciparum malaria. It is a process by which red blood cells containing mature parasites adhere to microvasculature (cytoadherence) and disappear from the circulation. As a result, late stages of the parasite are only sparsely detected in a peripheral blood slide, and when they do appear in significant numbers (>20% of the total parasites) this is a poor prognostic sign representing a large sequestered parasite load [26]. Autopsy studies show that sequestration is not distributed equally throughout the body and is greatest in the brain- particularly in the white matter, but also prominent in the heart, eyes, liver, kidneys, intestines, and adipose tissue [11].

The peripheral blood parasite count correlates poorly with the size of the sequestered biomass and the prognosis of severe malaria is thought to be related to this biomass [27]. Both light microscopic and electron microscopic studies have revealed that patients dying from cerebral malaria have more prominent sequestration in the brain microvasculature compared to severe but non-comatose fatal cases [28,29]. Sequestration is prominent in the cerebrum, cerebellum as well as the medulla oblongata. Autopsy studies in children dying from cerebral malaria in Malawi describe, in addition to erythrocyte sequestration, intravascular accumulation of platelets, which could play a role in cytoadherence [30,31].

Cytoadherence

This is mediated by a parasite derived protein called *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP-1). Under febrile conditions, which enhance expression, PfEMP-1 mediated cytoadhesion begins at approximately 12 hour of parasite development, 50% of the maximum effect is obtained at 14-16 hour, and adherence is highly effective in the second half of the parasite life cycle [26]. PfEMP-1 is encoded by highly variable VAR gene family, comprising around 60 genes. There is high switch rate of expression between these genes every new cycle, and this clonal antigenic variation helps the parasite in escaping the immune system. PfEMP-1 is expressed on the surface of RBC as 'knobs', which can be identified electron-microscopically as protrusions from the erythrocyte membrane acting as points of attachment to the vascular endothelium [26,32]. Cytoadherence is thought to reduce micro vascular blood flow, which may be responsible for organ and tissue dysfunction such as coma [33]. The metabolically active sequestered parasites may also deprive host tissues substrates (e.g. glucose) or produce toxins, especially during schizont rupture that disrupts host tissue metabolism [27].

Vascular endothelial ligands

Numerous receptors that can bind PfEMP-1 have been identified on vascular endothelium, with different distributions in various organs and different contributions to rolling, tethering and finally stable binding of the parasitized erythrocyte. Of these only CD36, which is constitutionally expressed on most vascular beds but remarkably absent in brain vessels, and chondroitin sulphate A, the main receptor in the placenta, are able to support firm adhesion under flow condition (this is responsible for infection in pregnant women). In severe malaria, as in other severe infections, blood concentrations of pro-

inflammatory cytokines like TNF- α , interleukin (IL)-1, IL-6 and IL-18 are raised, as well as anti-inflammatory Th2 cytokines (IL-4, IL-10), but there is an imbalance in patients with a fatal course of the disease [34]. Potent stimulator inducing pro-inflammatory cytokine productions by leucocytes are the glycosylphosphatidylinositol (GPI) anchors of *P. falciparum*. GPI stimulates the production of TNF- α and possibly also the lymphokine 'lymphotoxin' [26]. TNF is also suggested by some scientists to induce coma by stimulating the production of nitric oxide (NO) which interferes with synaptic transmission [35]. High circulating levels of NO are associated with severity, mortality and frequency of neurological sequelae in African children with severe malaria [24].

Rosetting

Binding of two or more uninfected RBCs to an infected RBC is called rosetting. Rosetting occurs in the middle of asexual life cycle. Rosetting is associated with cerebral malaria and cytoadherence with other vital organ dysfunctions. Rosetting encourages adherence and it is greater for blood groups A and B than blood group O. Rosetting may be inhibited by drugs like artemisinins and quinine (Artemisinin > Quinine) [14,36].

Deformability

As the parasite matures inside the RBC it becomes progressively more spherical and rigid [14]. Parasitized erythrocytes have reduced Red Cell Deformability (RCD), but more recently it has been shown that in patients with malaria, non parasitized red blood cells also have reduced RCD, which is associated with a poor outcome [37]. Impaired RCD may promote red blood cell destruction, as well as impairment of microcirculatory flow [27].

Recent discoveries in Pathogenesis of CM

There are increasing researches into the pathogenesis of CM and some of these will be briefly mentioned here. Severe malaria in children is associated with expression of specific PfEMP1 subtypes but the endothelial receptor for parasites expressing these proteins, previously unknown [38,39], has been identified as endothelial protein C receptor (EPCR) [40,41]. The PfEMP1 subtypes containing domain cassettes (DCs) 8 (group B/A hybrid) and 13 (group A) are shown to mediate adherence of *P. falciparum*-infected erythrocytes to brain endothelial cells [39,40]. A DC8-expressing clonal parasite line can also bind to primary microvascular cells from heart, lung, and dermis [39]. These observations suggest that DC8 and DC13 PfEMP1 variants play a key role in cytoadhesion of *P. falciparum*-infected erythrocytes to various endothelial cells. More recently, it has been demonstrated that the endothelial protein C receptor (EPCR) acts as an endothelial receptor for DC8 and DC13 PfEMP1 variants [41]. Furthermore, binding to human brain microvascular endothelial cells via EPCR is significantly higher in parasite isolates from patients with severe malaria than in those from children with uncomplicated and mild malaria [41].

Clinical Features of Cerebral Malaria

Cerebral malaria is one of the features of severe malaria which is a multisystemic disease. Severe malaria is mainly a paediatric disease in sub-Saharan Africa due to high transmission intensity [42]. Approximately one in ten adult patients develop significant intravascular haemolysis of both infected and uninfected erythrocytes

leading to haemoglobinuria ('black water fever'), causing anaemia and contributing to renal failure. Glucose-6-phosphate dehydrogenase deficiency is a predisposing factor to intravascular haemolysis [43]. Pregnant women are particularly vulnerable in both high and low transmission settings, with severe anaemia, hypoglycemia, coma, respiratory distress and pulmonary oedema as common features. In all patients with severe malaria metabolic acidosis is a frequent finding and it has a strong prognostic significance [44]. The three most consistent presenting complaints in CM from previous studies are fever, convulsions and loss of consciousness [45-48]. The clinical picture of cerebral malaria is that of a diffuse encephalopathy with unarousable coma; focal signs are relatively uncommon. In young children coma can develop rapidly, with a mean onset after only 2 days of fever, but sometimes just a few hours [45,46]. It is often heralded by one or more generalized seizures, which cannot be distinguished clinically from febrile convulsions. In adults the onset is usually more gradual, with high fever (mean duration of 5 days) and increasing drowsiness. The level of consciousness may fluctuate over a period of hours. Convulsions are present in about 15% of the adult cases, whereas more than 50% of paediatric cases have convulsions [45,46]. Convulsions are most frequently tonic-clonic generalized convulsions, but can also be Jacksonian type or focal. In small children approximately 25% have subtle or subclinical convulsions, with seizure activity on electroencephalography, but only minor convulsive movements of limbs or facial muscles [5]. These patients often have deviated eyes, upward rolling of the eyes, excessive salivation and irregular breathing patterns [46].

On neurological examination the febrile patient has no signs of meningism, although passive resistance to neck flexion is not uncommon and hyperextension of the neck may occur in severely ill patients [46]. The eyes often show a divergent gaze, with normal oculocephalic reflexes. Pupillary and corneal reflexes are usually normal but may be absent in deeply comatose children [46-48]. On fundoscopy, retinal haemorrhages can be observed in about 15% of cases [46-49]. These haemorrhages are boat or flame shaped and they seldom involve the macula. Areas of unusual retinal "whitening" and occasional cotton wool spots may also be seen [46,50].

Diagnosis

In clinical practice, the diagnosis of CM is based on finding asexual forms of *P. falciparum* in the peripheral blood of a febrile patient with unrousable coma lasting more than 30 minutes after seizures had stopped, for which no other cause was found by clinical and laboratory tests [47,51]. A high index of suspicion is required for the diagnosis of cerebral malaria in both endemic and non-endemic areas. Hypoglycemia, a common feature of severe malaria, should be ruled out and corrected. The principal differential diagnosis of CM in tropical areas is bacterial or viral meningoencephalitis especially in small children; this makes lumbar puncture for cerebrospinal fluid analysis a necessity. Diagnosis of cerebral malaria can be confirmed at autopsy by finding characteristic sequestered parasitized red blood cells in cerebral venules and capillaries [13,26,31,46,48]. The histopathologic hallmark of CM is sequestration of infected erythrocytes in the microcirculation of the brain and retina [52]. A postmortem study in Malawi by Taylor et al. [31] gave a further guide on how to accurately diagnose CM. The study showed that 23% of patients clinically diagnosed as CM actually died from other causes, and the remaining patients had parasites sequestered in cerebral capillaries.

It has also been shown that Retinopathy was the only clinical sign distinguishing malarial from non-malarial coma [31,50,52]. The retinal and cerebral circulations share a common embryologic origin, therefore changes identified by ophthalmoscopy at the fundus could be very helpful to accurately diagnose CM [53,54].

The diagnostic criteria for malaria retinopathy are: retinal hemorrhages, papilledema, an unusual discoloration of the retinal vessels, and a patchy whitening of the retina surrounding the fovea and in the periphery [52]. Malarial retinopathy is widely accepted as a diagnostic and prognostic factor in human cerebral malaria [53]. Furthermore, it has been recommended that retina examination be done routinely when CM is a possible diagnosis in a comatose child or adult [54].

Antimalarial Treatment

The mainstay of the treatment of cerebral and other forms of severe malaria is the immediate commencement of parenteral antimalarial treatment. Available drugs are injectable artesunate, quinine and artemether. Artesunate belongs to the group of the artemisinins, which are currently the most rapidly acting and potent available antimalarial drugs [51]. Unlike quinine they not only act on the mature form of the parasite, but also on the younger ring forms, preventing their maturation and sequestration. They also clear parasitaemia and fever faster than quinine [55-57]. The dose of artesunate is 2.4 mg/kg on admission, followed by the same dose after 12 and 24 hours and then daily until the patient is able to take oral medication. To prevent recrudescence of the infection, follow on medication should be given. Several regimens are possible, such as a full course of oral artemether-lumefantrine (Co-artem[®]) or a combination of oral artesunate (2 mg/kg per day, total course 7 days including the parenteral form) and amodiaquine (10 mg/kg per day for 3 days). Mefloquine is not recommended as maintenance antimalarial drug, because of its association with post-malaria neurological syndrome [58].

Supportive treatment

The usual nursing care for the unconscious patient should be applied (such as regular turning of the patient, hygienic eye care, passage of nasogastric tube and urethral catheter) [46]. Severe malaria is a multi-organ disease, and supportive treatment for all kinds of organ failure can be indicated. Anticonvulsant therapy, blood transfusion, fluid management and antibiotic should be individualized based on clinical and laboratory evidence [46].

Outcome of Cerebral Malaria

Death among hospitalized children with CM is often due to respiratory arrest and brainstem signs; most deaths occur within 24 hours of presentation in the hospital [45-47,49].

In surviving patients the median time to full recovery of consciousness is approximately 24 hours in children, compared to 48 hours in adults [59].

Neurological sequelae are rare in adults recovering from cerebral malaria (<1%) [26,46,60]. Encephalopathy and psychosis following cerebral malaria has been observed in 5% of adult patients taking mefloquine as oral follow on treatment, so it is advisable that mefloquine should not be used in cerebral malaria [46,58]. In children neurological residual abnormalities are more common, with approximately 12% still having symptoms at the moment of discharge,

including hemiplegia, cortical blindness, aphasia and cerebellar ataxia [45,59,61,62]. The prevalence of neurological deficits at discharge among survivors of CM ranges between 9 and 17.7% [45,47,59,60-64]. These symptoms often resolve completely over a period from one to six months in over half of the children, but a quarter will be left with major residual neurological deficits [47,62-64]. More subtle cognitive impairments as a late consequence of cerebral malaria is common in children, especially in those cases presenting with a combination of coma, hypoglycemia and seizures [60]. Even those who survive with no obvious neurological sequelae may have subtle cognitive deficiencies [60]. Furthermore, some sequelae (e.g. epilepsy and language impairment) have been reported and may only become evident later when the child starts going to school [62-64].

Conclusion

Cerebral malaria is a life threatening complication of malaria; it affects children more than adult. The mortality rate is high and a significant number of childhood survivors suffer from transient neurological deficit at discharge and subtle long-term cognitive deficiencies. High index of suspicion is needed for early diagnosis and effective treatment.

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