Pathophysiology, clinical presentation and treatment of cerebral malaria

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Abstract

Infection with Plasmodium falciparum can cause severe disease in the non-immune individual. Cerebral malaria is in most cases just one of the organs affected by the disease. The direct cause of coma in cerebral malaria remains obscure. A compromised microcirculation, with sequestration of parasitized erythrocytes, is central in the pathogenesis. Intravenous artesunate is superior to quinine in the treatment of severe malaria, possibly because of its broader stage specificity, preventing young ring forms to mature and sequester. Intravenous artesunate should become the treatment of choice in adults, and possibly also in children. Since multi organ involvement is very common, supportive treatment is essential to improve survival in this disease, which is responsible for more than one million deaths per year.

INTRODUCTION

Severe malaria is a potentially fatal disease. Rapid diagnosis and treatment is essential. It is a multi system disease, but cerebral malaria, characterized by unrousable coma, is one of the most common features. The direct cause of coma, which has a remarkable complete recovery in most of the surviving cases, is not known. This paper will review the pathophysiological and pathological changes associated with cerebral malaria, and the clinical presentation, diagnosis and treatment of this condition.

PATHOGENESIS

The parasite

Human malaria can be caused by Plasmodium falciparum, P. ovale, P. vivax and P. malariae, although clusters of malaria caused by P. knowlesi jumping species from long-tailed macaque monkeys to men have been described in Southeast Asia. The female Anopheles mosquito is the vector, injecting the sporozoite form of the parasite when probing for a blood meal. After inoculation the parasite hides and replicates in the liver for an average of 5.5 days in P. falciparum, after which 10^1 till 10^6 merozoites are released into the bloodstream. In malaria caused by P. vivax and P. ovale, but not P. falciparum, some parasites stay behind in the liver; these hypnozoites can cause a relapse of the disease long after treatment of the blood stage infection. The merozoites quickly invade circulating erythrocytes, where the erythrocytic cycle of the parasite begins. The parasite matures from a small ring form to the pigment containing trophozoite, and is named schizont after division of the nucleus. After 48 hours the erythrocyte ruptures and 6 to 36 merozoites are released, which will invade passing erythrocytes. This gives an exponential expansion of the infection in the human host, with a multiplication factor of around 10, but sometimes up to 20, per new generation, as observed in early studies with P. falciparum as a treatment for syphilis.  Thirteen days after inoculation the parasite number has increased from about 10 till 10^16 parasites, and the patient starts to have fever. In the non-immune patient the disease can quickly progress into severe disease if the infection is not treated, with an increase in the total number of parasites in the body up to 10^22 till 10^33.3

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Cytoadherence.

Although sporadically *P. vivax* is able to cause severe disease in humans, including pulmonary edema, haemoglobinuria and very rarely coma, the vast majority of severe disease is caused by *P. falciparum*. Yet this is also the only species that induces cytoadherence to vascular endothelium of erythrocytes containing the mature forms of the parasite. As the parasite matures, parasite proteins are transported and inserted into the erythrocyte membrane. The high molecular transmembrane protein *P. falciparum* erythrocyte membrane protein 1 or PfEMP1 is the most important ligand for cytoadherence. Under febrile conditions, which enhance expression, PfEMP1 mediated cytoadhesion begins at approximately 12 h of parasite development, 50% of the maximum effect is obtained at 14–16 h, and adherence is highly effective in the second half of the parasite life cycle. 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. PfEMP1 is encoded by the highly variable *VAR* gene family, comprising around 60 genes. The high switch rate between these genes gives rise to a new variant PfEMP1 in 2% of the parasites every new cycle, and this clonal antigenic variation helps the parasite escaping the immune system. PfEMP1 is expressed on the surface of ‘knobs’, which can be identified electron-microscopically as protrusions from the erythrocyte membrane acting as points of attachment to the vascular endothelium. Other surface proteins that might play a role in cytoadherence are rifin and sequestrin. On the vascular endothelium numerous receptors that can bind PfEMP1 have been identified, 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 (CSA), the main receptor in the placenta, are able to support firm adhesion under flow conditions. The intercellular adhesion molecule 1 (ICAM-1) is the most important receptor on brain endothelium, and its expression is upregulated by the pro-inflammatory cytokine TNF-α. Electrostatic forces are probably important in addition to steric factors in the binding of PfEMP1 to its receptors. Surface potential spectroscopy of ‘knobs’ has revealed that knobs are positively charged (+20 mV), whereas the endothelial plasma membranes and receptors have a negative surface charge. This could contribute to the promiscuity of PfEMP1 for a great variety of receptors. Recently it has been suggested that platelets, which express CD36, might serve as a sticky bridge between infected erythrocytes and the endothelium, which could be particularly important in the brain microvasculature lacking CD36. Cytoadherence causes sequestration of parasitized erythrocytes in the microcirculation, mainly capillaries and post-capillary venules. Autopsy studies show that sequestration is not distributed equally throughout the body and is greatest in the brain, but also prominent in the heart, eyes, liver, kidneys, intestines, and adipose tissue. It is also inhomogeneous in a specific vascular bed, with patent capillaries adjacent to vessels packed with sequestered parasitized erythrocytes. Both light microscopic and electron microscopic studies have found that patients dying from cerebral malaria have more prominent sequestration in the brain microvasculature compared to severe but non-comatose fatal cases. Sequestration is prominent in 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.

Red cell deformability, rosetting and auto-agglutination

Sequestration of parasitized erythrocytes will compromise the microcirculation in vital organs. In addition the deformability of both parasitized and uninfected erythrocytes is markedly reduced in severe malaria, and this is strongly associated with a fatal outcome of the disease. Acting synergistically with the reduction in lumen caused by sequestration, rigid erythrocytes presumably further reduce blood flow in the microcirculation of vital organs, causing dysosyxa with lactic acidosis, organ dysfunction and death. It should be noted that lactic acidosis is a strong and reproducible predictor for disease outcome in falciparum malaria, both in children and adults. In addition formation of erythrocyte clumps through rosetting and auto-agglutination could further compromise flow. Rosette formation is the *in vitro* phenomenon in which uninfected red blood cells adhere to erythrocytes containing the mature forms of the parasite. However, whereas
all erythrocytes containing the mature parasite cytoadhere, not all rosette.\textsuperscript{23,24} In epidemiological studies rosette forming strains have been associated with severe disease\textsuperscript{25,26,27}, whereas other studies have not found this association.\textsuperscript{28} The extent to which rosettes have a pathophysiologic role is not clearly established and will depend on their resistance to shear stresses encountered in the human circulation. Rosettes are quite resistant against pulling forces\textsuperscript{29}, but less against more physiologic shearing forces.\textsuperscript{30} A more recently described adherence property of parasitized red blood cells is the aggregation of parasitized red blood cells, which is mediated via platelet CD36. Presence of this phenotype has been associated with disease severity both in Kenya and in Thailand.\textsuperscript{31,32} Haemodynamic failure is in general not a contributor to microcirculatory failure. A low blood pressure is not a common feature of severe malaria. Cerebral blood flow is not decreased in cerebral malaria.\textsuperscript{33,34}

\textit{Permeability}

There is a mild generalized increase in the systemic vascular permeability in severe malaria, but the blood brain barrier (BBB) in adults with cerebral malaria is functionally grossly intact.\textsuperscript{35,36} Studies in African children with cerebral malaria do show a subtle increase in BBB permeability with a disruption of endothelial intercellular tight junctions on autopsy.\textsuperscript{37,38} Imaging studies reveal that most adults with cerebral malaria have no evidence of cerebral oedema.\textsuperscript{39,40} In African children cerebral oedema is more frequent, although not a consistent finding.\textsuperscript{41} Similarly, opening pressures on lumbar puncture are usually normal in adult patients, but are elevated in over 80\% of children with cerebral malaria.\textsuperscript{42,43} Part of the increase in intracranial pressure will be caused by the increased intracranial blood volume as a consequence of sequestration of parasitized erythrocytes. There are no published controlled trials evaluating the use of mannitol in cerebral malaria.\textsuperscript{44} However, a recent study in adults with cerebral malaria in India did not show a beneficial effect on coma or outcome (Dr S Mohanty, personal communication); a small series in Kenyan children with cerebral malaria showed that mannitol did lower intracranial pressure, but there was no control group with which to compare the benefit of mannitol on case fatality or neurological outcome. The exact role of raised intracranial pressure in the pathogenesis of coma in children is thus still unclear. Rather than a primary cause for coma it is more likely a feature developing in the later stages of the disease.

\textit{Cytokines}

In severe malaria, as in other severe infections, blood concentrations of proinflammatory cytokines like TNF-\(\alpha\), 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.\textsuperscript{45} A potent stimulator inducing proinflammatory cytokine production by leukocytes are the glycosylphosphatidylinositol (GPI) anchors of \textit{P. falciparum}.\textsuperscript{46} GPI stimulates the production of TNF-\(\alpha\) and possibly also the lymphokine 'lymphotoxin'. Both cytokines can upregulate the expression of ICAM-1 and VCAM-1 on endothelium cells, and could thus promote sequestration of parasitized erythrocytes in the brain, contributing to coma. High plasma concentrations of TNF-\(\alpha\) in patients with falciparum malaria correlate with disease severity, including coma, hypoglycaemia, hyperparasitaemia and death.\textsuperscript{47,48} However, a trial using monoclonal antibodies against TNF-\(\alpha\) did not show a beneficial effect on either mortality or coma duration. In fact its use was associated with a significant increase in neurological sequelae. Moreover concentrations of TNF-\(\alpha\) are equally high in paroxysms of uncomplicated vivax malaria as in patients with severe falciparum malaria. Further downstream in the cytokine cascade, nitric oxide (NO) production is increased via inducible NO synthase (iNOS) in patients with severe malaria. NO has been proposed as a cause for coma because of its ability to interfere with neurotransmission.\textsuperscript{49} Results from clinical studies measuring metabolites of NO show conflicting results\textsuperscript{50,51}, which does not necessarily disprove the hypothesis, since current methods are too insensitive to detect more subtle local NO overproduction. Inducible nitric oxide synthase expression is increased in the brain in fatal cerebral malaria.\textsuperscript{52} More recently other cytokines like high-mobility group box protein1 (HMGB1) have been implicated in the pathogenesis of cerebral malaria, but their role has to be further defined.\textsuperscript{53} Also the importance of intravascular accumulation of monocytes that has been described in autopsy studies needs further study.\textsuperscript{54,55} With our present knowledge pro-inflammatory cytokines seem to be related to overall disease severity, and are clearly involved in the pathogenesis of fever and possibly other complications like adult respiratory distress syndrome (ARDS), but not in the
pathogenesis of coma per se. Other researchers in the field contest this view.\textsuperscript{55}

What is the cause of coma in cerebral malaria?

A conclusive pathophysiological model explaining the reversible coma of cerebral falciparum malaria does not exist. 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.\textsuperscript{32} Reduced red cell deformability and sticky forces 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 NO or yet to be evaluated other cytokines might impair neurotransmission, but their roles remain hypothetical. Axonal accumulation of $\beta$-amyloid precursor protein as a measure of impaired axonal transport has become evident from autopsy studies and may represent a final common pathway leading to in essence reversible neurological dysfunction in cerebral malaria.\textsuperscript{56} Whether focal dysoxia is the cause of this axonal dysfunction is not established.

CLINICAL FEATURES

Severe malaria is a multisystem disease, cerebral involvement is one of the features. In a recent large treatment trial in predominantly adult patients with severe malaria in Southeast Asia, 54\% of the 1050 patients with strictly defined severe malaria had cerebral malaria, and only 16\% had cerebral symptoms without any other organ involvement.\textsuperscript{57} Mortality in this last group was 19\%, compared to up to 43\% when multiple organs were involved. These numbers are different in sub-Saharan Africa, where due to the high transmission intensity severe malaria is mainly a paediatric disease.\textsuperscript{58} Main symptoms in children are severe anaemia, hypoglycaemia and coma with convulsions. In Southeast Asia, where transmission is much lower and protective immunity is not acquired, all age groups can get severe malaria, but young adults are the most affected group. Cerebral malaria, renal failure, severe jaundice and adult respiratory distress syndrome are the main complications in this group. 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.\textsuperscript{59} Pregnant women are particularly vulnerable in both high and low transmission settings, with severe anaemia, hypoglycaemia, coma, and pulmonary oedema as common features. In all patients with severe malaria metabolic acidosis is a frequent finding and is important to assess since it has a strong prognostic significance.\textsuperscript{22} Kussmaul type respiration can be a warning symptom for this.\textsuperscript{58} Acidosis is mainly, but not entirely, caused by increased lactic acid production as a result of anaerobic glycolysis.\textsuperscript{22,60} In case of renal failure, acid-base homeostasis will be further compromised. Shock is not a common feature of severe malaria and should alert the clinician for the possible concomitant presence of septicemia.

Neurological symptoms in cerebral malaria

The clinical picture is that of a diffuse encephalopathy with unrousable 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.\textsuperscript{61} 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. Occasionally frankly psychotic behaviour is the first manifestation of cerebral involvement. The level of consciousness may fluctuate over a period of hours. Convulsions are present in about 15\% of the cases, whereas more than 50\% of paediatric cases have convulsions.\textsuperscript{57,61} 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.\textsuperscript{62} These patients often have deviated eyes, excessive salivation and irregular breathing patterns.

On neurological examination the febrile patient has no signs of meningism, although passive resistance to neck flexion is not uncommon and hyperreflexion of the neck may occur in severely ill patients. The eyes often show a divergent gaze, with normal oculocephalic reflexes. Pupil and corneal reflexes are usually normal. On fundoscopy retinal haemorrhages can be observed in about 15\% of cases.\textsuperscript{63} In areas of high
transmission (Sub-Saharan Africa) a high background prevalence of peripheral parasitaemia can hamper the diagnosis of ‘cerebral malaria’. A positive blood slide in a febrile comatose child does not always adequately exclude other possible diagnoses in this setting. The presence of retinal haemorrhages can sometimes be useful here because of its specificity for malaria.20 Cranial nerve involvement in patients with cerebral malaria is rare. Bruxism with grinding of the teeth and a positive pout reflex are common in cases with deep coma. Muscle tone and tendon reflexes are often increased, but can also be normal or reduced. An ankle and less frequently a patellar clonus can sometimes be evoked. Abdominal reflexes are absent and the plantar reflexes are extensor in approximately half of the cases. Various forms of abnormal posturing can be present, with either a decorticate pattern with flexor rigidity of the arms and extension of the legs or a decerebrate pattern with abnormal extensor responses in arms and legs with or without opisthotonos.64

In surviving patients the median time to full recovery of consciousness is approximately 24 hours in children, compared to 48 hours in adults. Neurological sequelae are rare in adults recovering from cerebral malaria (<1%).57 Encephalopathy and psychosis following cerebral malaria has been observed in 5% of cases taking mefloquine as oral follow on treatment, so that this drug should not be used in this setting. However, parasitemia and parasite stages cannot be assessed in this way. PfHRP2 remains circulating weeks after cure, which can result in false positive results in high transmission settings in patients with a recent malaria attack. Hypoglycaemia, a common feature of severe malaria, should be ruled out. The principal differential diagnosis in tropical areas is of a bacterial or viral meningoencephalitis. If the patient presents with any sign of meningeal involvement a lumbar puncture should be performed. Especially in small children this implies that in most cases a lumbar puncture will be necessary. Some African centres treating paediatric cerebral malaria postpone lumbar puncture fearing herniation related to raised intracranial pressure which is present in a majority of their cases. These centres start empiric antibiotic coverage in all children until results of lumbar puncture become available.

**Antimalarial treatment**

The mainstay of the treatment of severe and cerebral malaria is the immediate start of parenteral antimalarial treatment. Available drugs are injectable artemunate, quinine and artemether. Intravenous chloroquine has become obsolete in Asia and almost the whole rest of the world because of widespread resistance of the parasite to this once so successful drug. Artemisunate belongs to the group of the artemisinins, which are currently the most rapidly acting and potent available antimalarial drugs. 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.50 A recent large multicenter multinational randomized trial in 1461 mainly adult patients in Southeast Asia
has clearly established the superiority of intravenous artesunate over quinine in the treatment of severe malaria.\textsuperscript{57} Mortality was 35% lower in the artesunate treated patients compared to quinine. In the patients with cerebral malaria the mortality difference was 7%. Treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia. Since children were underrepresented in the Asian trial, a similar trial is currently performed in African children to determine if artesunate should become the treatment of choice not only in adults but also in children. 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\textsuperscript{6}), or a combination of oral artesunate (2 mg/kg per day, total course 7 days including the parenteral form) and doxycyclin (4 mg/kg per day for 7 days, contraindicated in small children and pregnant women). Mefloquine is not recommended as maintenance antimalarial drug, because of its association with post-malaria neurological syndrome.\textsuperscript{65}

Until parenteral artesunate becomes more widely registered and available in more countries most patients in Asia will currently still be treated with parenteral quinine. Although quinine resistance has increased in areas of Southeast Asia and South America, there is still no high-grade resistance in severe malaria that precludes its use. Quinine has a narrow therapeutic ratio and should never been given by bolus injection, which can lead to fatal hypotension. A loading dose of 20 mg base/kg over 4 hours should be given by controlled infusion. The loading dose is followed by a dose of 30 mg base/kg/24hours, as a continuous infusion or in 3 divided doses of 10 mg/kg, each given over 4 hours time. The pharmacokinetic properties of quinine alter in severe malaria: the volume of distribution is reduced, whereas the binding to plasma proteins is increased. Plasma clearance is reduced proportional to severity of disease.\textsuperscript{71} Consequently, doses should be reduced by 30 to 50% after the third day of treatment to avoid accumulation of the drugs in patients who remain seriously ill. In the presence of severe kidney or liver failure, the dose reduction should be effectuated after the second day of treatment.\textsuperscript{64} If there is a history of mefloquine or quinine treatment within the 24 hours before admission, no loading dose of quinine should be given, since this can increase the cardiotoxic effects of the drug. The total course is seven days of quinine. Quinine can be switched to the oral formulation, using the same dose of 10 mg/kg t.i.d., if the patient is able to eat. Similar to patients treated with artesunate, this should be combined with doxycyclin, except in small children or pregnant women in order to reduce the risk of recrudescence. Alternatively quinine can be discontinued and a full course of artemether-lumefantrine can be given after the patient is able to eat. Minor adverse reactions are common with quinine therapy and consist of the symptom complex known as cinchonism, with tinnitus, high tone deafness, nausea, uneasiness, malaise and blurring of vision. A side effect that has important consequences for patient management is the induction of hypoglycaemia by quinine through its potent effect on pancreatic insulin secretion. Monitoring, at least every 3 hours, of plasma glucose levels is therefore indicated during treatment with quinine. Severe life-threatening adverse effects, such as hypotension, myocardial conduction disturbance, blindness, deafness, and coma are rare and related to plasma doses above 20 mg/l, which should not be reached during treatment with the recommended scheme.

A third alternative is intramuscular artemether in a dose of 3.2 mg/kg on admission, followed by a daily dose of 1.6 mg/kg. Clinical trials comparing artemether with quinine show that artemether is safe and easier to use than quinine but overall survival is similar and not statistically significantly better than quinine.\textsuperscript{72} Artemether is an oil-based formulation, which releases drug slowly and erratically from the injection site.\textsuperscript{73} In some patients, particularly in those who are severely ill, artemether may not be absorbed for up to 12 hours after injection. Because of these pharmacokinetic disadvantages parenteral artemether is not the artemisinin derivative of choice for the treatment of severe malaria.

**Supportive treatment**

Patients with coma will need endotracheal intubation and mechanical ventilation to protect the airway, if this facility is available. The usual nursing care for the unconscious patient should be applied (such as regular turning, nasogastric tube, eye care, urethral catheter). Convulsions are very common in children with cerebral malaria, but choice and dose of a seizure prophylactic.
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Benefits of blood transfusion should outweigh the risks (esp. HIV and other pathogens). In children, severe malaria, but most prominently in young children. Anaemia is present in almost all patients with severe malaria, but less so in adult Asian patients. A recent study in Kenyan children showed that positive bacterial blood cultures are present in 20% of children admitted with a diagnosis of severe malaria. The threshold for starting antibiotics should therefore be low. If the patient has been admitted for several days in the i.c.u., hospital acquired infections can also be expected. Secondary pneumonia is common.

**Anaemia** is present in almost all patients with severe malaria, but most prominently in young children. Benefits of blood transfusion should outweigh the risks (esp. HIV and other pathogens). In adults the threshold for blood transfusion can be set at a hematocrit below 20%. In children the African guidelines are to give transfusion below a haemoglobin concentration of 5 g/dl in combination with respiratory distress, impaired conscious or hyperparasitaemia or an absolute cut-off of 4 mg/dl.

Oliguric renal failure is a common complication of severe malaria in adults, although non-oliguric renal failure also occurs. The clinical features resemble acute tubular necrosis and dialysis is a life saving procedure in these patients. Continuous veno-venous hemofiltration has proven to be superior to peritoneal dialysis. Renal function returns after a median of four days, although some patients will require dialysis for more than a week.

**Blackwater fever** with severe intravascular hemolysis can cause severe anemia requiring transfusion. Alkalisation of the urine to protect the kidney can be recommended in this condition, although no clinical studies are available. ARDS is a feared complication in adult patients with a high mortality rate, and can still develop in the days after admission. The patient should be propped upright and receive oxygen therapy. Furosemide should be tried to lower the venous pressure, but this will generally not sufficiently relieve symptoms, since the pathogenesis is capillary leakage and not fluid overload as such. In almost all cases the patient will require invasive mechanical ventilation in order to have a chance to survive. ‘Permissive hypercapnia’ cannot be used as a ventilation strategy, since this will further increase intracranial pressure in the already engorged brain.

Despite optimal treatment, the mortality of severe malaria remains high. Many adjunctive treatments have been proposed, but thus far none of them has proven to be beneficial. An exception should perhaps be made for exchange transfusion. Exchange transfusion has been used since 1974 with some encouraging results, but no randomized trials are available to prove its benefits. Exchange transfusion quickly removes circulating parasites, but the pathophysiological important sequestered biomass is not available for exchange. However, recent studies suggest that the benefit from exchange transfusion results from replacing the rigid, non-deformable, unparasitized red cells.

No consensus about the indications of exchange transfusion exists. Hyperparasitemia above 30% or above 10% in the presence of severe disease, or the presence of bad prognostic signs like a high plasma lactate, irrespective of parasitemia, can be regarded as an indication. If applied, fluid overload should be prevented.
CONCLUSION

Cerebral malaria is a common presentation of severe falciparum malaria. It is characterized by coma without focal signs and complete recovery is remarkable in the majority of surviving cases. The pathogenesis of coma remains obscure; coma could be neuroprotective in this state of compromised blood supply. Reduced microcirculatory flow caused by sequestration of parasitized erythrocytes and rigid erythrocytes is central in the pathophysiology of severe disease. A recent trial has proven that intravenous artesunate should become the treatment of choice in adults with severe and cerebral malaria; a similar trial in children is under way. Supportive treatment tailored to the patient’s specific organ dysfunctions is essential in this multi-system disease, ideally in an intensive care unit setting. Adjunctive treatments have thus far not proven to be beneficial. Even if optimal treatment is available, mortality rates remain high once the patient develops severe disease. Prevention strategies and early diagnosis and treatment with effective antimalarial drugs in the public health sector are therefore equally important.

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REFERENCES


