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REVIEW ARTICLES

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.[1] 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 10^5 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 meroizoites 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.[2] Thirteen days after inoculation the parasite number has increased from about 10 till 10^{10} 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^{12} till 10^{13}.[3]

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Cytoadherence.

Although sporadically *P. vivax* is able to cause severe disease in humans, including pulmonary edema[4], haemoglobinuria and very rarely coma[5], 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 *Pf*EMP1 is the most important ligand for cytoadherence.[6] Under febrile conditions, which enhance expression, P*f*EMP1 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.[7] 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.[8] *Pf*EMP1 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 *Pf*EMP1 in 2% of the parasites every new cycle, and this clonal antigenic variation helps the parasite escaping the immune system.[9] P*f*EMP1 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[10] and sequestrin.[11] On the vascular endothelium numerous receptors that can bind P*f*EMP1 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.[12] The intercellular adhesion molecule 1 (ICAM-1) is the most important receptor on brain endothelium[13], 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 *Pf*EMP1 to its receptors. Surface potential spectroscopy of 'knobs' has revealed that knobs are positivily charged (+20 mV), whereas the endothelial plasma membranes and receptors have a negative surface charge.[14] This could contribute to the promiscuity of *Pf*EMP1 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.[15] 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.[16] 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.[17,18] 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.[19,20]

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.[21] Acting synergistically with the reduction in lumen caused by sequestration, rigid erythocytes presumably further reduce blood flow in the microcirculation of vital organs, causing dysoxya 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.[22] 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.[23,24] In epidemiological studies rosette forming strains have been associated with severe disease[25,26,27], whereas other studies have not found this association.[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[29], but less against more physiologic shearing forces.[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.[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.[33,34]

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.[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.[37,38] Imaging studies reveal that most adults with cerebral malaria have no evidence of cerebral oedema.[39,40] In African children cerebral oedema is more frequent, although not a consistent finding.[41] Similarly, opening pressures on lumbar puncture are usually normal in adult patients, but are elevated in over 80% of children with cerebral malaria.[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.[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.

Cytokines

In severe malaria, as in other severe infections, blood concentrations of proinflammatory cytokines like TNF-α, 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.[45] A potent stimulator inducing proinflammatory cytokine production by leucocytes are the glycosylphosphatidylinositol (GPI) anchors of *P. falciparum.*[46] GPI stimulates the production of TNF-α 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-α in patients with falciparum malaria correlate with disease severity, including coma, hypoglycaemia, hyper-parasitaemia and death.[47,48] However, a trial using monoclonal antibodies against TNF-α 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-α 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.[49] Results from clinical studies measuring metabolites of NO show conflicting results[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.[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.[53] Also the importance of intravascular accumulation of monocytes that has been described in autopsy studies needs further study.[37,54] 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.[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.[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 β-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.[56] Whether focal dysoxya 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.[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.[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.[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.[22] Kussmaul type respiration can be a warning symptom for this.[58] Acidosis is mainly, but not entirely, caused by increased lactic acid production as a result of anaerobic glycolysis.[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.[61] It is often heralded by one or more generalized seizures, which cannot be distinguished clinically from febrile convulsions. In adults the onset in 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.[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.[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.[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.[65] 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.[66] These symptoms will completely resolve over a period from 1 till 6 months in over half of the children, but a quarter will be left with a major residual neurological deficits. 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, hypoglycaemia and seizures.[67]

DIAGNOSIS AND TREATMENT

Diagnosis

Since the disease is so common in the tropical world, cerebral malaria should be considered in every comatose patient with a history of fever who has been in a malarious area in the previous two months. The diagnosis should be confirmed by microscopy of stained thin and thick blood films, at a magnification of 1000. The intraerythrocytic parasites have to be identified and counted. In severe malaria, the developmental stage of the parasites and the percentage of neutrophils containing malarial pigment should also be noted, since these have prognostic significance.[8,68] A negative blood smear makes the diagnosis very unlikely, but if there is still uncertainty the test should be repeated every 12 hours for 48 hours. Microscopy with fluorescent staining of the buffy coat (quantitative buffy coat analysis or QBC) has a higher sensitivity to detect low parasitemias, but this is seldom needed. Dipstick detection of the *P. falciparum* antigens *Pf*HRP2 and *p*LDH (Parasight-F, ICT Malaria Pf, OptiMAL), have a diagnostic sensitivity similar to that of microscopy, but do not require an experienced microscopist.[69] However, parasitemia and parasite stages cannot be assessed in this way. *Pf*HRP2 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 meningo-encephaltits. 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 artesunate, 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. Artesunate 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.[70] 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.[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^{R}), 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.[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.[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.[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.[72] Artemether is an oil-based formulation, which releases drug slowly and erratically from the injection site.[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

drug has not been well established and is currently not recommended. A study in Kenyan children showed increased mortality using an i.m. dose of 20 mg/kg phenobarbitone. This was presumably caused by respiratory depression in these non-ventilated children, since mortality was greatest in those receiving two or more doses of diazepam.[74] In adults convulsions are much less common. If seizures occur high flow oxygen and appropriate airway management should be initiated. Convulsions can be treated with either i.v lorazepam (0.1 mg/kg) or if no vascular access is available rectal diazepam (0.5 mg/kg). If repeated doses are not effective, rectal paraldehyde can be given (0.4 mg/kg) and treatment with an intravenous loading dose of phenytoin (18 mg/kg over 20 min) or phenobarbital (15-20 mg/kg over 10 min) can be initiated.[75] Since children are prone to febrile convulsions, treatment to reduce fever should be given if the rectal temperature is above 39×C. Hypoglycaemia as a contributing factor, which is particularly common in children, pregnant women and with quinine use, should be ruled out.

Severe malaria is a multi-organ disease, and supportive treatment for all kinds of organ failure can be indicated. *Fluid management* can be difficult. The patient is usually dehydrated on admission, and should be rehydrated to support the already compromised microcirculation. However, overhydration should be avoided since there is a strong tendency to develop pulmonary edema, especially in adult patients and pregnant women. A central venous line or Swan-Ganz catheter can be inserted to guide fluid management. Hypotension not responding to a fluid bolus is not common, and circulatory shock is suggestive for concurrent septicemia. *Concomitant bacterial infection* is common in African children 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.[76] 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.[64] *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.[77] 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. Alkalinisation 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 relief 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.[78] 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 micro-circulatory 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

1. Singh B, Kim Sung L, Matusop A, Radhakrishnan A, Shamsul SS, Cox-Singh J, Thomas A, Conway DJ. A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings. *Lancet* 2004; 363: 1017-24.
2. Fairley NH. Sidelights on malaria in man obtained by sub-inoculation experiments. *Trans R Soc Trop Med Hyg* 1947; 40: 621–76.
3. Dondorp AM, Desakorn V, Pongtavornpinyo W, Sahassananda D, Silamut K, Chotivanich K, Newton PN, Pitisuttithum P, Smithyman AM, White NJ, Day NP. Estimation of the total parasite biomass in acute falciparum malaria from plasma PfHRP2. *PLoS Med* 2005; 2: e204.
4. Pukrittayakamee S, Chantra A, Vanijanonta S, White NJ. Pulmonary oedema in vivax malaria. *Trans R Soc Trop Med Hyg* 1998; 92: 421-2.
5. Kochar DK, Saxena V, Singh N, Kochar SK, Kumar SV, Das A. *Plasmodium vivax* malaria. *Emerg Infect Dis* 2005; 11: 132-4.
6. Magowan C, Wollish W, Anderson L, Leech J. Cytoadherence by *Plasmodium falciparum* infected erythrocytes is correlated with expression of a family of variable proteins on infected erythrocytes. *J Exp Med* 1988; 168: 1307-20.
7. Udomsangpetch R, Pipitaporn B, Silamut K, Pinches R, Kyes S, et al. Febrile temperatures induce cytoadherence of ring-stage *Plasmodium falciparum*–infected erythrocytes. *Proc Natl Acad Sci USA* 2002; 99: 11825–9.
8. Silamut K, White NJ. Relation of the stage of parasite development in the peripheral blood to prognosis in severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1993; 87: 436–43.
9. Roberts DJ, Craig AG, Barendt AR, Pinches R, Nash G, Marsh K, Newbold CI. Rapid switching to multiple antigenic and adhesive phenotypes in malaria. *Nature* 1992; 357: 689-92.
10. Kyes SA, Rowe JA, Kriek N, Newbold CI. Rifins: a second family of clonally variant proteins expressed on the surface of red cells infected with *Plasmodium falciparum*. *Proc Natl Acad Sci USA* 1999; 96: 9333-8.
11. Ockenhouse CF, Klotz FW, Tandon NN, Jamieson GA. Sequestrin, a CD36 recognition protein on *Plasmodium falciparum* malaria-infected erythrocytes identified by anti-idiotype antibodies. *Proc Natl Acad Sci USA* 1991; 88: 3175-9.
12. Cooke B, Coppel R, Wahlgren M. Falciparum malaria: sticking up, standing out and out-standing. *Parasitol Today* 2000; 10: 416-20.
13. Turner GDH, Morrison H, Jones M, Davis TM, Looareesuwan S, Buley ID, Gatter KC, Newbold CI, Pukritayakamee, S, Nagachinta B, White NJ. An immunohistochemical study of the pathology of fatal malaria. Evidence for widespread endothelial activation and a potential role for intercellular adhesion molecule-1 in cerebral sequestration. *Am J Path* 1994; 145, 1057-69.
14. Aikawa M, Kamanura K, Shiraishi S, Matsumoto Y, Arwati H, Torii M, Ito Y, Takeuchi T, Tandler B. Membrane knobs of unfixed *Plasmodium falciparum* infected erythrocytes: new findings as revealed by atomic force microscopy and surface potential spectroscopy. *Exp Parasitol* 1996; 84: 339-43.
15. Wassmer SC, Lepolard C, Traore B, Pouvelle B, Gysin J, Grau GE. Platelets reorient *Plasmodium falciparum*-infected erythrocyte cytoadhesion to activated endothelial cells. *J Infect Dis* 2004; 189: 180-9.
16. MacPherson GG, Warrell MJ, White NJ, Looareesuwan S, Warrell DA. Human cerebral malaria: a quantitative ultrastructural analysis of parasitized erythrocyte sequestration. *Am J Path* 1985; 119, 385-401.
17. Silamut K, Phu NH, Whitty C, Turner GD, Louwrier K, Mai NT, Simpson JA, Hien TT, White NJ. A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain. *Am J Path* 1999; 155: 395-419.
18. Pongponratn E, Turner GD, Day NP, Phu NH, Simpson JA, Stepniewska K, Mai NT, Viriyavejakul P, Looareesuwan S, Hien TT, Ferguson DJ, White NJ. An ultrastructural study of the brain in fatal *Plasmodium falciparum* malaria. *Am J Trop Med Hyg* 2003; 69: 345-59.
19. Grau GE, Mackenzie CD, Carr RA, Redard M, Pizzolato G, Allasia C, Cataldo C, Taylor TE,

Molyneux ME. Platelet accumulation in brain microvessels in fatal pediatric cerebral malaria. *J Infect Dis* 2003; 187: 461-6.
20. Taylor TE, Fu WJ, Carr RA, Whitten RO, Mueller JS, Fosiko NG, Lewallen S, Liomba NG, Molyneux ME. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. *Nat Med* 2004; 10: 143-5.
21. Dondorp AM, Kager PA, Vreeken J, White NJ. Abnormal blood flow and red cell deformability in severe falciparum malaria. *Parasit Today* 2000; 16: 228-32.
22. Day N, Phu NP, Mai NTH, et al. Prognostic significance of acidosis in severe malaria. *Crit Care Med* 2000; 28: 1833-40.
23. Udomsangmetch R, Wahlin B, Carlson J, Berzins K, Torii M, Aikawa M, Perlman P, Wahlgren M. *Plasmodium falciparum*-infected erythrocytes form spontaneous erythrocyte rosettes. *J Exp Med* 1989; 169: 1835-40.
24. David PH, Handunetti SM, Leech JH, Gamage P, Mendis KN. Rosetting: a new cytoadherence property of malaria infected erythrocytes. *Am J Trop Med Hyg* 1988; 38: 289-97.
25. Carlson J, Helmby H, Hill AVS, Brewster D, Greenwood BM, Wahlgren M. Human cerebral malaria: association with erythrocyte rosetting and lack of anti-rosetting antibodies, *Lancet* 1990; 336: 1457-60.
26. Ringwald P, Peyron F, Lepers JP, Rabarison P, Rakotomalala C, Razanamparany M, Rabodonirina M, Roux J, Lebras J. Parasite virulence factors during falciparum malaria: rosetting, cytoadherence, and modulation of cytoadherence by cytokines. *Infect Immun* 1993; 61: 5198-204.
27. Rowe A, Obeiro J, Newbold CI, Marsh K. *Plasmodium falciparum* rosetting is associated with malaria severity in Kenya. *Infect Immun* 1995: 63: 2323-6.
28. Al-Yaman F, Genton B, Mokela D, Raiko A, Kati S, Rogerson S, Reeder J, Alpers M. Human cerebral malaria: lack of significant association between erythrocyte rosetting and disease severity. *Trans R Soc Trop Med Hyg* 1995; 89: 55-8.
29. Nash GB, Cooke BM, Carlson J, Wahlgren M. Rheological properties of rosettes formed by red blood cells parasitized by *Plasmodium falciparum*. *BrJ Haematol* 1992; 82: 757-63.
30. Chotivanich KT, Dondorp AM, White NJ, Peters K, Vreeken J, Kager PA, Udomsangpetch R. The resistance to physiological shear stresses of the erythrocytic rosettes formed by cells infected with *Plasmodium falciparum*. *Ann Trop Med Parasit* 2000; 94: 219-26.
31. Pain A, Ferguson DJ, Kai O, Urban BC, Lowe B, Marsh K, Roberts DJ. Platelet mediated clumping of *Plasmodium falciprum*-infected erythrocytes is a common adhesive phenotype and is associated with severe malaria. *Proc Natl Acad Sci USA* 2001; 98: 1805-10.
32. Chotivanich K, Sritabal J, Udomsangpetch R, Newton P, Stepniewska KA, Ruangveerayuth R, Looareesuwan S, Roberts DJ, White NJ. Platelet-induced autoagglutination of *Plasmodium falciparum*-infected red blood cells and disease severity in Thailand. *J Infect Dis* 2004; 189: 1052-5.
33. Warrell DA, White NJ, Veall N, Looareesuwan S, Chanthavanich P, Phillips RE, Karbwang J, Pongpaew P. Cerebral anaerobic glycolysis and reduced cerebral oxygen transport in human cerebral malaria. *Lancet* 1988; 2: 534-8.
34. Clavier N, Rahimy C, Falanga P, Ayivi B, Payen D. No evidence for cerebral hypoperfusion during cerebral malaria. *Crit Care Med* 1999; 27: 628-32.
35. Davis TM, Suputtamongkol Y, Spencer JL, Ford S, Chienkul N, Schulenburg WE, White NJ. Measures of capillary permeability in acute falciparum malaria: relation to severity of infection and treatment. *Clin Infect Dis* 1992; 15: 256-66.
36. Warrell DA, Looareesuwan S, Phillips RE, White NJ, Warrell MJ, Chapel HM, Areekul S, Tharavanij S. Function of the blood-cerebrospinal fluid barrier in human cerebral malaria: rejection of the permeability hypothesis. *Am J Trop Med Hyg* 1986; 35: 882-9.
37. Brown H, Rogerson S, Taylor T, Tembo M, Mwenechanya J, Molyneux M, Turner G. Blood-brain barrier function in cerebral malaria in Malawian children. *Am J Trop Med Hyg* 2001; 64: 207-13.
38. Adams S, Brown H, Turner G. Breaking down the blood-brain barrier: signaling a path to cerebral malaria? *Trends Parasitol* 2002; 18: 360-6.
39. Looareesuwan S, Warrell DA, White NJ, Sutharasamai P, Chanthavanich P, Sundaravej K, Juel-Jensen BE, Bunnag D, Harinasuta T. Do patients with cerebral malaria have cerebral oedema? A computed tomography study. *Lancet* 1983; 1: 434-7.
40. Looareesuwan S, Wilairatana P, Krishna S, Kendall B, Vannaphan S, Viravan C, White NJ. Magnetic resonance imaging of the brain in patients with cerebral malaria. *Clin Infect Dis* 1995; 21: 300-9.
41. Newton CR, Peshu N, Kendall B, Kirkham FJ, Sowunmi A, Waruiru C, Mwangi I, Murphy SA, Marsh K. Brain swelling and ischaemia in Kenyans with cerebral malaria. *Arch Dis Child* 1994; 70: 281-7.
42. White NJ. Lumbar puncture in cerebral malaria. *Lancet* 1991; 338: 640-1.
43. Newton CR, Kirkham FJ, Winstanley PA, Pasvol G, Peshu N, Warrell DA, Marsh K. Intracranial pressure in African children with cerebral malaria. *Lancet* 1991; 337:573-6.
44. Okoromah CA, Afolabi BB. Mannitol and other osmotic diuretics as adjuncts for treating cerebral malaria. *Cochrane Database Syst Rev* 2004; 4: CD004615.
45. Day NP, Hien TT, Schollaardt T, Loc PP, Chuong LV, Chau TT, Mai NT, Phu NH, Sinh DX, White NJ, Ho M. The prognostic and pathophysiologic role of pro- and antiinflammatory cytokines in severe malaria. *J Infect Dis* 1999; 180: 1288-97.
46. Channe Gowda D. Structure and activity of glycosylphosphatidylinositol anchors of *Plasmodium falciparum*. *Microbes Infect* 2002; 4: 983-90.
47. Grau GE, Taylor TE, Molyneux ME, Wirima JJ, Vassalli P, Hommel M, Lambert PH. Tumor necrosis

factor and disease severity in children with falciparum malaria. *N Engl J Med* 1989; 320: 1586-91.
48. Kwiatkowski D, Hill AV, Sambou I, Twumasi P, Castracane J, Manogue KR, Cerami A, Brewster DR, Greenwood BM. TNF concentration in fatal cerebral, non-fatal cerebral, and uncomplicated *Plasmodium falciparum* malaria. *Lancet* 1990; 336: 1201-04.
49. Clark IA, Rockett KA, Cowden WB. Possible central role of nitric oxide in conditions clinically similar to cerebral malaria. *Lancet* 1992; 340: 894-6.
50. Al Yaman FM, Mokela D, Genton B, Rockett KA, Alpers MP, Clark IA. Association between serum levels of reactive nitrogen intermediates and coma in children with cerebral malaria in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1996; 90: 270-3.
51. Dondorp AM, Planche T, de Bel EE, Angus BM, Chotivanich K, Silamut K, Ruangveerayuth R, Hoek F, Romijn J, Kager PA, Vreeken J, White N J. Nitric oxides in plasma, urine and cerebrospinal fluid in patients with severe falciparum malaria. *Am J Trop Med Hyg* 1998; 59: 497-502.
52. Maneerat Y, Viriyavejakul P, Punpoowong B, Jones M, Wilairatana P, Pongponratn E, Turner GD, Udomsangpetch R. Inducible nitric oxide synthase expression is increased in the brain in fatal cerebral malaria. *Histopathology* 2000; 37: 269-77.
53. Alleva LM, Yang H, Tracey KJ, Clark IA. High mobility groupbox 1(HMGB1) protein: possible amplification signal in the patho-genesis of falciparum malaria. *Trans R Soc Trop Med Hyg* 2005; 99: 171-4.
54. Patnaik JK, Das BS, Mishra SK, Mohanty S, Satpathy SK, Mohanty D. Vascular clogging, mononuclear cell margination, and enhanced vascular permeability in the pathogenesis of human cerebral malaria. *Am J Trop Med Hyg* 1994; 51: 642-7.
55. Clark IA, Alleva LM, Mills AC, Cowden WB. Pathogenesis of malaria and clinically similar conditions. *Clin Microbiol Rev* 2004; 17: 509-39.
56. Medana IM, Day NP, Hien TT, Mai NT, Bethell D, Phu NH, Farrar J, Esiri MM, White NJ, Turner GD. Axonal injury in cerebral malaria. *Am J Path* 2002; 160: 655-66.
57. The South East Asian Quinine Artesunate Malaria Trial (Seaquamat) Group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* 2005; 366: 717-25.
58. Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, Marsh V, Newton C, Winstanley P, Warn P, Peshu N, Pasvol G, Snow R. Indicators of life-threatening malaria in African children. *N Engl J Med* 1995; 332: 1399-404.
59. Tran TH, Day NP, Ly VC, Nguyen TH, Pham PL, Nguyen HP, Bethell DB, Dihn XS, Tran TH, White NJ. Blackwater fever in southern Vietnam: a prospective descriptive study of 50 cases. *Clin Infect Dis* 1996; 23: 1274-81.
60. Dondorp AM, Thi Hong Chau T, Hoan Phu N, Thi Hoang Mai N, Phu Loc P, Van Chuong L, Xuan Sinh D, Taylor A, Tinh Hien T, White NJ, Day NPJ. Unidentified acids of strong prognostic significance in severe malaria. *Crit Care Med* 2004; 32: 1683-8.
61. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 1989; 71: 441-59.
62. Crawley J, Smith S, Kirkham F, Muthinji P, Waruiru C, Marsh K. Seizures and status epilepticus in childhood cerebral malaria. *Q J Med* 1996; 89: 591-7.
63. Looareesuwan S, Warrell DA, White NJ, Chanthavanich P, Warrell MJ, Chantaratherakitti S, Changswek S, Chongmankongcheep L, Kanchanaranya C. Retinal hemorrhage, a common sign of prognostic significance in cerebral malaria. *Am J Trop Med Hyg* 1983; 32: 911-5.
64. WHO. Severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2000; 94 (Suppl 1): 1-90.
65. Nguyen TH, Day NP, Ly VC, Waller D, Nguyen HP, Bethell DB, Tran TH, White NJ. Post-malaria neurological syndrome. *Lancet* 1996; 348: 917-21.
66. Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. *Lancet* 1990; 336: 1039-43.
67. Holding PA, Stevenson J, Peshu N, Marsh K. Cognitive sequelae of severe malaria with impaired consciousness. *Trans R Soc Trop Med Hyg* 1999; 93: 529-34.
68. Nguyen PH, Day N, Pram TD, Ferguson DJ, White NJ. Intraleucocytic malaria pigment and prognosis in severe malaria. *Trans R Soc Trop Med Hyg* 1995; 89: 200-4.
69. Moody A. Rapid diagnostic tests for malaria parasites. *Clin Microbiol Rev* 2002; 15: 66-78.
70. ter Kuile F, White NJ, Holloway P, Pasvol G, Krishna S. *Plasmodium falciparum*: in vitro studies of the pharmacodynamic properties of drugs used for the treatment of severe malaria. *Exp Parasitol* 1993; 76: 85-95.
71. White NJ, Looareesuwan S, Warrell DA, Warrell MJ, Bunnag D, Harinasuta T. Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. *Am J Med* 1982; 73: 564-72.
72. Artemether-Quinine Meta-analysis Study Group. A meta-analysis using individual patient data of trials comparing artemether with quinine in the treatment of severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2001; 95: 637-50.
73. Hien TT, Davis TM, Chuong LV, Ilett KF, Sinh DX, Phu NH, Agus C, Chiswell GM, White NJ, Farrar J. Comparative pharmacokinetics of intramuscular artesunate and artemether in patients with severe falciparum malaria. *Antimicrob Agents Chemother* 2004; 48: 4234-9.
74. Crawley J, Waruiru C, Mithwani S, Mwangi I, Watkins W, Ouma D, Winstanley P, Peto T, Marsh K. Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. *Lancet* 2000; 355: 701-6.
75. Maitland K, Nadel S, Pollard AJ, Williams TN, Newton CR, Levin M. Management of severe malaria in children: proposed guidelines for the United Kingdom. *BMJ* 2005; 331: 337-43.

76. Berkley JA, Lowe BS, Mwangi I, Williams T, Bauni E, Mwarumba S, Ngetsa C, Slack MP, Njenga S, Hart CA, Maitland K, English M, Marsh K, Scott JA. Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med* 2005; 352: 39-47.
77. Phu NH, Hien TT, Mai NT, Chau TT, Chuong LV, Loc PP, Winearls C, Farrar J, White N, Day N. Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. *N Engl J Med* 2002; 347: 895-902.
78. Dondorp AM, Nyanoti M, Mithwani S, Vreeken J,. Kager PA, Marsh K. The role of reduced red cell deformability in the pathogenesis of severe falciparum malaria and its restoration by blood transfusion. *Trans R Soc Trop Med Hyg* 2002; 96: 282-7.