REVIEW

Cerebral malaria

N. J. White
Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand and Centre for Tropical Medicine, Nuffield Department of Clinical Medicine; E-mail: nickw@tropmedres.ac
Practical Neurology, 2004, 4, 20–29

Malaria is the most important parasitic disease of man. It infects approximately 5% of the world's population and kills somewhere between one and two million people each year. Of the four species of malaria parasites that infect humans, only *Plasmodium falciparum* is lethal. Cerebral involvement causing coma in severe falciparum malaria is a characteristic but ominous development carrying a 15–20% treated case fatality. Untreated it is considered uniformly fatal. Cerebral malaria is widely quoted as being the most common cause of coma in tropical areas of the world.

WHO GETS CEREBRAL MALARIA?

In some parts of the tropics malaria is acquired as many as two or three times every day and thus everyone in the community has malaria all the time. At the other end of the spectrum, there are many areas where the chances of acquiring malaria are relatively low. For example, along the western border of Thailand, falciparum malaria is acquired on average only once every 2 years – but in these areas malaria is still a major cause of morbidity and mortality.

The clinical manifestations of malaria differ considerably depending on the intensity of malaria transmission. In low transmission settings, symptomatic malaria occurs at all ages and cerebral malaria occurs both in adults and in children. Pregnant women are at greater risk of developing severe disease. In contrast, in high transmission settings, severe malaria is confined to the first few years of life. Cerebral malaria is the major presentation of severe malaria in low and medium transmission settings, but when malaria transmission is very intense it is less common, and occurs almost exclusively in infants and young children. Non-immune visitors of any age who travel to malarious areas are at significant risk.

Cerebral malaria results from continued parasite multiplication in an uncomplicated infection – it is therefore a consequence of late treatment. Anti-malarial drugs taken for prophylaxis will not prevent malaria parasites being aquired, but

© 2004 Blackwell Publishing Ltd

Pract Neurol: first published as 10.1111/j.1474-7766.2004.05-199.x on 1 February 2004. Downloaded from http://pn.bmj.com/ on January 21, 2022 by guest. Protected by copyright.

Pract Neurol: first published as 10.1111/j.1474-7766.2004.05-199.x on 1 February 2004. Downloaded from http://pn.bmj.com/ on January 21, 2022 by guest. Protected by copyright.

if effective, they do stop the infection developing to levels that produce symptoms and disease.

PATHOLOGY

The essential pathological feature of cerebral malaria is that the capillaries and venules of the brain are densely packed with red blood cells containing mature stages of *Plasmodium falciparum* (Marchiafava & Bignami 1894; Silamut *et al*. 1999) (Fig 1). This process, known as sequestration, results from the cytoadherence of the parasitized red cells to vascular endothelium. The infected red cells express an adhesive protein on their surface that glues them to the endothelial lining of the blood vessels. Thus the brain is engorged with static, space occupying, parasitized red cells that obstruct the microcirculation. In severe malaria the situation is further compromised by a general reduction in red cell deformability (this is a specific pathological process that does not occur in sepsis), which impairs the ability of the circulating erythrocytes to squeeze past the adherent parasitized cells. Cerebral oedema is not a major pathological process (Looareesuwan *et al*. 1995; Newton *et al*. 1994). The pattern of sequestration is heterogeneous with some capillaries and venules blocked, while adjacent vessels may be completely unaffected (it has many mathematical similarities to urban traffic congestion!). This probably explains why permanent anoxic-ischaemic damage is relatively uncommon despite abundant evidence of hypoperfusion. White matter vessels are more affected than grey matter vessels, and there is histological and biochemical evidence of disrupted axonal function (Medana *et al*. 2002).

CLINICAL FEATURES

The clinical hallmark of malaria is fever. Indeed malaria is so common in tropical countries that it is usually the first diagnosis in anyone presenting with fever. In the returned traveller presenting with fever, malaria must always be excluded. In young children the progression from mild fever to severe illness can be rapid (typically a 1–3 day history), whereas in older children and adults there is usually a history of several days fever and illness before the development of cerebral symptoms and signs (WHO 2000; Newton & Krishna 1998).

In children, coma is often heralded by one or more generalized convulsions. These cannot be distinguished clinically from febrile convulsions – indeed there is overlap as children with falciparum malaria are more likely to have isolated seizures than children with comparable levels of fever caused by other infections or even vivax malaria. In adults, the onset may be more insidious with high fever and increasing drowsiness. Some adults, particularly young fit males, may present initially with fever and aggressive behaviour or marked irritability. Occasionally frankly psychotic behaviour is the first manifestation of cerebral involvement. Progression thereafter tends to be rapid with the development of unrousable coma within hours. Strictly defined, cerebral malaria refers to the development of unrousable coma, which cannot be attributed to another pathological process in a patient with falciparum malaria. From a practical perspective, any unusual behaviour or any deterioration in the level of consciousness in a patient with falciparum malaria indicates cerebral involvement, and the patient should be treated for severe malaria.

On general examination

The patient is febrile, unrousable, and may be anaemic as a result of haemolytic destruction of both parasitized and non-parasitized red cells (Newton *et al*. 2000). Jaundice is more common in adults and may be deep – the differential diagnosis then includes fulminant viral hepatitis, severe leptospirosis, or sepsis. There is no rash, no petechiae, and other signs of a bleeding diathesis are very unusual all of which helps to differentiate cerebral malaria clinically from the viral haemorrhagic fevers. Vital signs are usually normal with warm vasodilated peripheries, a low to normal blood

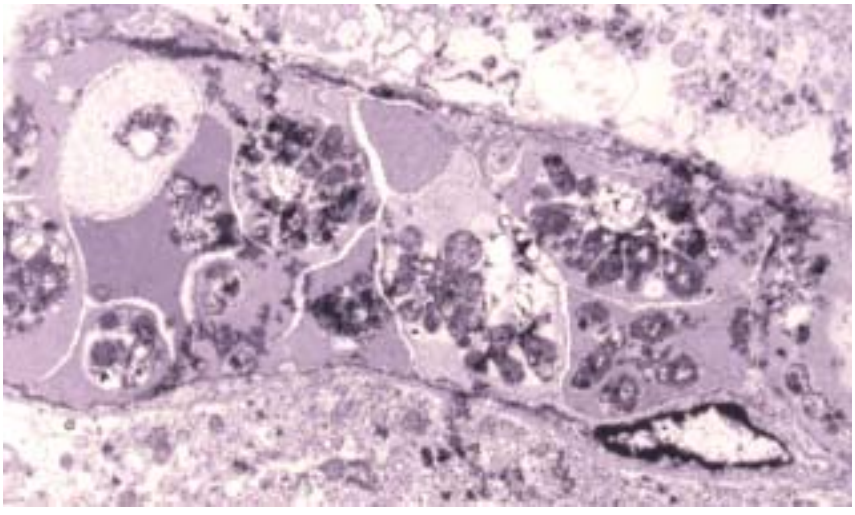

Figure 1 Electron micrograph of a cerebral vessel in fatal cerebral malaria. The red cells are tightly packed, adherent to the vascular endothelium, and each contains a mature parasite.

© 2004 Blackwell Publishing Ltd

pressure, and sinus tachycardia – although shock may occur. The respiratory rate is often increased. Acidotic (Kussmaul's) breathing is an ominous sign because metabolic acidosis is a particularly severe manifestation of falciparum malaria and one that carries a high mortality. Clinical examination may reveal splenomegaly and hepatomegaly (massive splenomegaly is rare – and argues against the diagnosis) and is often otherwise entirely normal. Children who are obtunded with fever and respiratory distress (acidotic breathing) may be misdiagnosed initially as having pneumonia.

Differentiation from meningo-encephalitis

The principal differential diagnosis in tropical areas is of a bacterial or viral meningo-encephalitis. In cerebral malaria there may be some passive resistance to neck flexion but this is easily distinguished from 'true meningism'. Nevertheless, for inexperienced physicians the distinction may be uncertain – and a lumbar puncture should be performed in most cases. The CSF is clear (or if yellow is usually the result of hyperbilirubinaemia not a cerebral haemorrhage). The mean pressure in adults and children is approximately 16 cm; 20% of adults and 80% of children (in whom the normal range is lower) have raised pressures but very high opening pressures are unusual (White 1991).

Examination of the nervous system

The level of consciousness varies and may fluctuate over a period of hours. The eyes are commonly divergent but cranial nerve involvement is rare (and when present is usually a VIth nerve palsy) (WHO 2000; Newton & Krishna 1998; Newton *et al*. 2000). Fundoscopy is often difficult because of roving eye movements, but can be rewarding. Approximately 15% of patients have readily seen retinal haemorrhages sometimes with pale centres. Indirect ophthalmoscopy reveals haemorrhages and other abnormalities in a much higher proportion of cases. Cotton wool spots and characteristic areas of retinal whitening may be seen, and occasionally segmental hypoperfusion of retinal microvessels is observed (reflecting sequestration of parasitized red cells containing little haemoglobin) (Lewallen *et al*. 1999). Papilloedema or retinal oedema are rare, but serious signs if present. The pupils are mid-size and equally reactive. The corneal reflexes are usually preserved – their absence indicates a poor prognosis. The oculocephalic and caloric reflexes are preserved. Bruxism and a positive pout reflex are common but other 'frontal release' signs are rare. The tone in the limbs is often increased, but may be normal or decreased. The jaw jerk may be positive and the limb reflexes are correspondingly brisk with extensor plantar responses in approximately half the cases.

Seizures are very common in children and occur in about 15% of adults. They are usually grand mal in type, but focal seizures may also occur. Patients may present in status epilepticus. Subtle continuous seizure activity is common, particularly in children. A proportion of children are unconscious directly as a result of continued seizure activity, which may be manifest only by tonic-clonic eye movements or excess salivation. Extensor posturing, sometimes associated with hyperventilation, cutaneous vasoconstriction, and gooseflesh are all relatively common.

Sustained hyperventilation (acidotic breathing, respiratory distress) is a serious sign as it indicates metabolic acidosis.

In adults, the Glasgow coma scale is used to assess coma, and in children the simpler Blantyre scale is used (cerebral malaria; score ≤ 2, normal = 5) (Table 1). In survivors the onset and offset of coma in children is quicker than in adults with a median time to full recovery of consciousness of approximately 24 h compared with 48 h in adults. Coma recovery can be protracted; some 10% of adults do not reach a GCS of 15 within one week.

Case fatality

In children approximately 50% of deaths occur within 12 h, and 80% within 36 h, whereas in adults over 50% of deaths occur after 24 h in hospital. Although the overall case fatality of cerebral malaria is approximately 15–20%, this is commonly related to multiple vital organ dysfunction and acidosis – 'pure' cerebral malaria carries a lower mortality (7–8%) (WHO 2000; Newton & Krishna 1998; Newton *et al*. 2000).

Other severe manifestations

The spectrum of severe manifestations of malaria differs in adult and children (see Table 2). Children are more likely to develop severe anaemia, to have generalized or focal seizures, and they are less likely than adults to become jaundiced, and they rarely develop acute renal failure or pulmonary oedema (WHO 2000).

Approximately half of all adults with cerebral malaria have evidence of renal impairment. This is an important determinant of outcome.

© 2004 Blackwell Publishing Ltd

Pract Neurol: first published as 10.1111/j.1474-7766.2004.05-199.x on 1 February 2004. Downloaded from http://pn.bmj.com/ on January 21, 2022 by guest. Protected by copyright.

Table 1 Comparison of the Blantyre coma scale for children with the Glasgow coma scale for adults

THE BLANTYRE COMA SCALE FOR CHILDREN	SCORE[a]	THE MODIFIED GLASGOW COMA SCALE FOR ADULTS	SCORE[b]
Best motor response		**Best motor response**	
Localizes painful stimulus[c]	2	Obeys commands	6
Withdraws limb from pain[d]	1	Localizes pain	5
Non-specific or absent response	0	Withdrawal to pain	4
		Flexion to pain	3
		Extension to pain	2
		None	1
Verbal response		**Verbal response**	
Appropriate cry	2	Oriented	5
Moan or inappropriate cry	1	Confused	4
None	0	Inappropriate words	3
		Incomprehensible sounds	2
		None	1
Eye movements		**Eyes open**	
Directed (e.g. follows mother's face)	1	Spontaneously	4
Not directed	0	To speech	3
		To pain	2
		Never	1

[a]Total score ranges from 0 to 5; 2 or less indicates 'unrousable coma'.
[b]Total score ranges from 3 to 15; 'Unrousable coma' reflected in a score of < 9.
[c]Painful stimulus: rub knuckles on patient's sternum.
[d]Painful stimulus: firm pressure on thumbnail bed with horizontal pencil.

Table 2 Complications of cerebral malaria

COMPLICATION	PATHOGENESIS	MANAGEMENT
Recurrent seizures/status	Cerebral sequestration of parasitized erythrocytes	Anticonvulsants, but ventilate if risk of respiratory arrest.
Acute renal failure	Acute tubular necrosis	Early haemofiltration/dialysis
Acute pulmonary oedema	As in adult respiratory distress syndrome – unknown. Myocardial function relatively unimpaired	Early positive pressure ventilation
Hypoglycaemia	Increased glucose turnover, reduced gluconeogenesis, quinine stimulated hyperinsulinaemia	Bolus then continuous 10% glucose infusion. Monitor plasma glucose frequently
Metabolic acidosis	Multifactorial; mainly lactic acidosis ± renal impairment	Rehydration; early haemofiltration/dialysis
Severe anaemia/haemoglobinuria ('blackwater fever')	Haemolysis of parasitized and unparasitized cells	Transfuse with fresh blood; do not stop antimalarial treatment
Septicaemia	Possibly compromise of gut barrier	Broad spectrum antibiotics

© 2004 Blackwell Publishing Ltd

Pract Neurol: first published as 10.1111/j.1474-7766.2004.05-199.x on 1 February 2004. Downloaded from http://pn.bmj.com/ on January 21, 2022 by guest. Protected by copyright.

The pathology is acute tubular necrosis – not glomerulonephritis – and it recovers eventually.

Patients with severe malaria may become shocked. This can result directly from malaria itself (algid malaria), or from supervening septicaemia. Severe malaria predisposes to invasive bacterial infections.

Hypoglycaemia is common (25% of children and 8% of adults) and multifactorial. It is often unsuspected and so the blood glucose concentration must be monitored frequently. On admission, hypoglycaemia is associated with severe disease and metabolic (lactic) acidosis, and is a poor prognostic sign. Insulin levels are appropriately suppressed. But after 24 h of treatment, hypoglycaemia results usually from an entirely separate pathology – quinine induced hyperinsulinaemia (White *et al*. 1983). This tends to be recurrent. Iatrogenic hypoglycaemia is particularly common in pregnant women (50% of cases).

Acidosis is also multifactorial. Lactic acidosis and renal failure are the two main contributors, but sometimes ketoacidosis and salicylates play a role (English *et al*. 1997; Day *et al*. 2000). The plasma lactate or the plasma bicarbonate concentration are probably the best overall measures of disease severity in malaria (Day *et al*. 2000) (Table 3).

DIAGNOSIS

Thick and thin blood smears should be taken, stained and read as soon as possible – do not delay! (See Fig 2.) The film contains important prognostic information. The number of red blood cells (RBC) containing a parasite per 1000 RBC is counted first on the thin film. If the count is low, the thick film is examined for the number of parasites per 200 white cells. The higher the parasite count, the more mature the parasite stages (if > 20% of parasites contain visible pigment – the brown black product of haemo-

Table 3 Laboratory indicators of a poor prognosis in cerebral malaria

Haematology
Leucocytosis › 12000/μL
Severe anaemia PCV ‹ 15%
Coagulopathy
Platelets ‹ 50 000/μL
Prothrombin time prolonged › 3 s
Prolonged partial thromboplastin time
Fibrinogen ‹ 200 mg/dL
Blood film
Hyperparasitaemia › 500 000/μL
› 20% of parasites are pigment-containing trophozoites and schizonts
› 5% of neutrophils contain visible malaria pigment
Biochemistry
Major
Hypoglycaemia ‹ 2.2 mmol/L
Hyperlactataemia › 5 mmol/L
Acidosis – Arterial pH ‹ 7.3, serum HCO_3 ‹ 15 mmol/L
Serum creatinine › 265 μmol/L[a]
Minor
Total bilirubin › 50 μmol/L
Liver enzymes – SGOT (AST) ≥ 3 × upper limit of normal
Muscle enzymes – SGPT (ALT) ≥ 3 × upper limit of normal
Urate › 600 μmol/L

PCV, packed cell volume; SGOT (AST), serum glutamic oxaloacetic transferase (aspartate aminotransferase); SGPT (ALT), serum glutamic pyruvic transaminase (alanine aminotransferase).

[a]Serum creatinine: this is the criterion for adults. Less elevated values are found in children with severe malaria.

© 2004 Blackwell Publishing Ltd

Pract Neurol: first published as 10.1111/j.1474-7766.2004.05-199.x on 1 February 2004. Downloaded from http://pn.bmj.com/ on January 21, 2022 by guest. Protected by copyright.

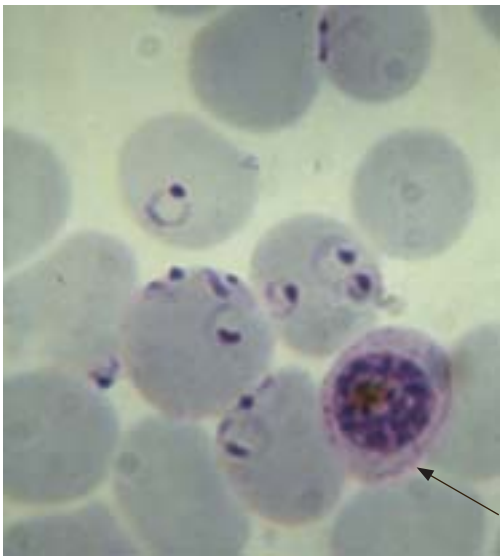

Figure 2 The peripheral blood film in a patient with cerebral malaria. The parasitaemia is very high; most of the parasites are at the ring stage which circulate freely, but one (arrow) is at the mature schizont stage (parasitised erythrocytes such as this are mostly sequestered in the capillaries and venules).

globin digestion), and the more neutrophils that contain phagocytosed malaria pigment (> 5%) the worse the prognosis.

There are now several rapid simple stick tests that detect malaria antigen in blood (PfHRP2 or PfLDH). They take a few minutes, are as sensitive as microscopy, but they do not provide prognostic information.

It is *extremely* unusual for a patient with cerebral malaria to have a negative blood smear. When it does happen it is the result of previous antimalarial treatment – but in such cases the PfHRP2 tests are still positive. So if the smear and PfHRP2 tests are negative – the patient has another cause for their coma.

MANAGEMENT

As in any other seriously ill unconscious patient, cerebral malaria requires intensive care management. Vital signs and core temperature should be measured frequently. Electrocardiographic monitoring is not essential (unless parenteral quinidine is used for treatment, as in the USA, or the patient has underlying heart disease). Myocardial function is not compromised significantly in severe malaria (unlike sepsis) and arrhythmias are rare. The patient should be catheterized, oxygenation monitored by pulse oximetry, and urine output monitored hourly. Accurate fluid balance is essential, particularly in adults where pulmonary oedema may develop with normal pulmonary artery occlusion pressures (adult respiratory distress syndrome). Many patients are 'dry' on admission. Central venous pressure monitoring is helpful to avoid subsequent fluid overload.

The initial assessment should be rapid, and includes a blood smear for diagnosis and prognosis, assessment of the level of consciousness and vital signs, resuscitation, and starting parenteral antimalarial treatment based on estimated or measured weight. It is essential that the first (loading) dose of antimalarial treatment be given correctly without delay. Once the patient has stabilized, intravenous access has been secured, antimalarial drug treatment has started, and initial laboratory investigations have been sent, a more detailed and less hurried examination should then be performed.

If there is biochemical evidence of acute renal impairment or severe acidosis, then haemofiltration should be started early because this is associated with a reduction in case fatality (Phu *et al*. 2002).

There is no trial evidence, but my clinical impression is that early positive pressure ventilation may also be of benefit. Respiratory arrest is a common cause of death, and is made more likely by the use of anticonvulsants. The development of hypoxia results usually from pulmonary oedema, or aspiration pneumonia. Pulmonary oedema is associated with normal left-sided filling pressures (i.e. results from pulmonary vascular leakage rather than myocardial dysfunction) and should be treated with positive pressure ventilation. Intubation should be performed rapidly and smoothly because with an engorged brain (packed with static cytoadherent parasitized red cells) there is little intracranial space to accommodate vasodilatation resulting from hypercapnoea. Coning is

© 2004 Blackwell Publishing Ltd

Pract Neurol: first published as 10.1111/j.1474-7766.2004.05-199.x on 1 February 2004. Downloaded from http://pn.bmj.com/ on January 21, 2022 by guest. Protected by copyright.

unusual in cerebral malaria, but may follow a difficult and protracted attempt at intubation.

Because hypoglycaemia is so common, and there are often no accompanying signs in an already comatose patient, the plasma glucose must be checked at a minimum of 4 h intervals, and rechecked if there is any unexplained clinical deterioration. A sudden fall in the level of consciousness may result either from hypoglycaemia, or supervening bacterial septicaemia (when it is often associated with hypotension). In such patients, if plasma glucose is normal, then empirical broad spectrum antibiotic treatment should be started as soon as blood cultures have been taken. If the patient is found to be hypoglycaemic, then there is often a disappointing response to parenteral glucose with little or no immediate improvement in the level of consciousness.

Severe malaria is associated with the rapid development of anaemia so blood grouping is a wise measure on admission. The indication for transfusion depends on the availability of blood. Fresh blood is best. In South-east Asia, a haematocrit of 20% or below is used as an indicator for transfusion, but in Africa, where blood for transfusion is more scarce, 15% has been used. Case fatality rises with haematocrit below 15%. Bleeding or massive haemoglobinuria should be managed with fresh blood transfusion. In the past there has been overdiagnosis of 'anaemic heart failure' in children in endemic areas with malaria, severe anaemia, and respiratory distress. These children are acidotic and need blood transfusion urgently (English *et al*. 1997).

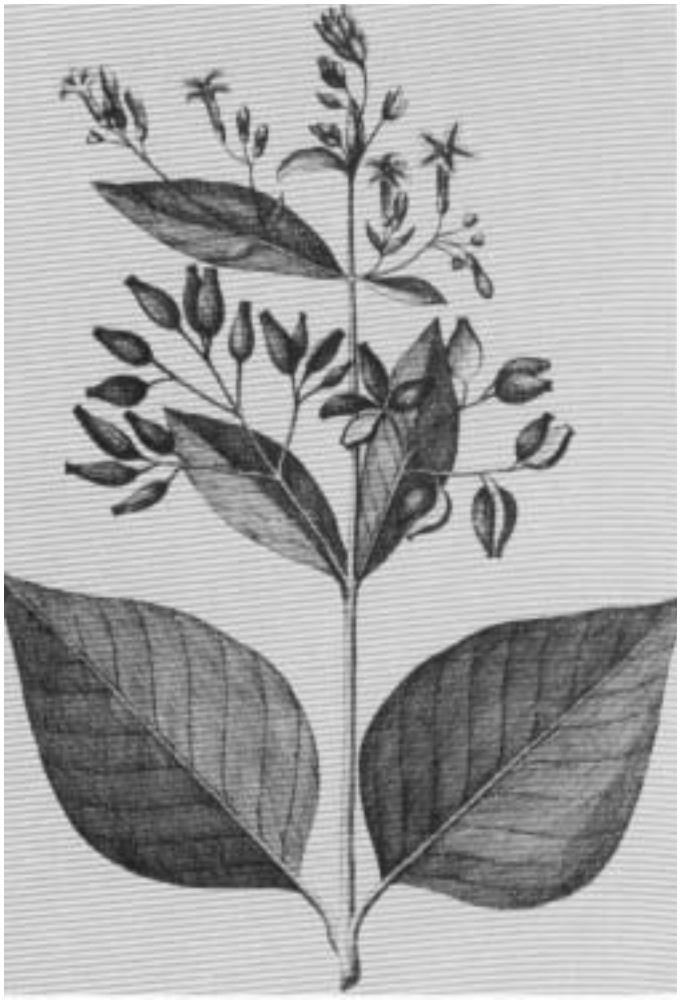

Figure 3 Cinchona, the tree from which quinine is extracted.

DRUG TREATMENT

Antimalarial drugs

The Cinchona alkaloid quinine is still the most widely used drug in the world for the treatment of severe malaria. In the USA, the dextrorotatory diastereomer quinidine is used instead because it is more widely available. This alkaloid is more difficult to use because it commonly produces prolongation of the electrocardiographic QT interval, and hypotension. However, the Cinchona alkaloids are increasingly being replaced by a different plant product originating in China. The artemisinin (Qinghaosu) derivatives, artesunate and artemether, are as effective as quinine (indeed they may be more effective) and they are simpler to administer and safer.

General points

- Do not use chloroquine because most *P. falciparum* infections are now chloroquine-resistant.
- Infusions can be given in 0.9% saline, 5% or 10% dextrose.
- Infusion rates for quinine or quinidine should be carefully controlled.
- Oral treatment should start as soon as the patient can swallow reliably enough to complete a full course of treatment.

Quinine should be given in an initial loading dose ([Table 4). When in doubt, the loading dose should always be given unless there is clear evidence that the patient has received adequate pretreatment with quinine. The risks of undertreatment outweigh those of overtreatment. There is really no convincing evidence that quinine causes adverse cardiac effects at plasma concentrations within the therapeutic range (8–15 mg/L), even in elderly patients with underlying cardiac disease. On the other hand

© 2004 Blackwell Publishing Ltd

Pract Neurol: first published as 10.1111/j.1474-7766.2004.05-199.x on 1 February 2004. Downloaded from http://pn.bmj.com/ on January 21, 2022 by guest. Protected by copyright.

undertreatment is potentially lethal. If there is no significant clinical and laboratory evidence of improvement, the maintenance doses of quinine should be reduced by one-third to one-half after 48 h of treatment to prevent drug accumulation. Otherwise the dose regimen should be unchanged. The doses of artemisinin derivatives are given in Table 4.

Quinine causes a number of minor adverse effects (collectively termed 'cinchonism'), evident on recovery of consciousness, which include tinnitus, nausea, dysphoria, and high tone hearing loss. Although quinine self-poisoning is associated with blindness from direct retinal toxicity, deafness, blindness or cardiovascular abnormalities are very rare following the treatment of malaria (WHO 2000). Persistent blindness or deafness are nearly always associated with overdose and are very unusual with correct dosing. Iatrogenic hypoglycaemia, on the other hand, is common, and is the most important adverse effect of quinine treatment (it also occurs with quinidine, but not the artemisinin derivatives).

Other than rare type 1 hypersensitivity reactions, artemisinin derivatives have no serious adverse effects. Artesunate can be given by bolus intravenous or intramuscular injection and artemether is given only by intramuscular injection. Artesunate is preferable because the water-soluble drug is instantly bioavailable, whereas absorption of artemether from intramuscular injection is slow and erratic. Large randomised trials comparing artemether and quinine have shown a case fatality benefit in South-east Asian adults, but not in African children, in favour of artemether (The Artemether-Quinine Meta-analysis Study Group 2001). Large trials with artesunate, which has better pharmacokinetic properties, are now in progress. Unfortunately parenteral artesunate and artemether are not usually available outside tropical countries.

When the patient can swallow reliably and safely, oral treatment may be substituted, and a full course of treatment completed. This will depend on local antimalarial treatment policies. Three-day courses of artemether-lumefantrine or atovaquone-proguanil, or 7- day courses of either artesunate or quinine plus doxycycline (or clindamycin in children and pregnant women) will give over 90% cure rates everywhere.

Anticonvulsants

Convulsions should be treated with standard anticonvulsants in the usual way. The prevention of convulsions is more controversial since a large double-blind placebo controlled trial of prophylactic phenobarbitone (20 mg/kg i.m) in Kenyan children showed an increased case fatality in the phenobarbitone group (Crawley *et al.*

Table 4 Antimalarial treatment of cerebral malaria

HOSPITAL INTENSIVE CARE UNIT	HEALTH CLINIC NO INTRAVENOUS INFUSIONS POSSIBLE
Quinine	
Initial dose: Quinine dihydrochloride 7 mg salt/kg infused over 30 min followed immediately by 10 mg/kg over 4 h Or 20 mg salt/kg infused over 4 h. Maintenance dose: 10 mg salt/kg infused over 2–8 h at 8-h intervals[a]	Quinine dihydrochloride 20 mg salt/kg diluted 1 : 2 with sterile water given by split injection into both anterior thighs. Maintenance dose: 10 mg/kg 8-hourly[a]
OR IF QUININE IS NOT AVAILABLE	
Quinidine	
10 mg base/kg infused over 1–2 h followed by 1.2 mg base/kg per hour.[b] Electrocardiographic monitoring advisable	
Artemisinin derivatives	
Artemether 3.2 mg/kg stat. by i.m. injection followed by 1.6 mg/kg daily	As for hospital ICU: artesunate can also be given by i.m. injection
Artesunate 2.4 mg/kg stat. by i.v. injection followed by 1.2–2.4 mg/kg daily	Artesunate suppositories; 10 mg/kg stat then daily

[a]The preferred dosage interval for parenteral quinine in African children is 12 h.

[b]Some authorities recommend a lower dose of quinidine; 6.2 mg base/kg initially over 1 h followed by 0.75 mg base/kg per hour.

© 2004 Blackwell Publishing Ltd

Pract Neurol: first published as 10.1111/j.1474-7766.2004.05-199.x on 1 February 2004. Downloaded from http://pn.bmj.com/ on January 21, 2022 by guest. Protected by copyright.

starting severely ill children, with repeated convulsions, on anticonvulsants may cause lethal depression of the respiratory centre

2000). There was an interaction with multiple doses of diazepam, and the main cause of death was acute respiratory arrest. This suggests that starting severely ill children, with repeated convulsions, on anticonvulsants may cause lethal depression of the respiratory centre. This may be circumvented by elective positive pressure ventilation, which then allows adequate anticonvulsant treatment to be given, particularly in children

Other drugs

Many adjuvant therapies have been suggested in the treatment of cerebral malaria, based on the prevailing pathophysiology hypothesis of the time. These include heparin, low molecular weight dextran, mannitol, urea, high-dose corticosteroids, aspirin, prostacyclin, pentoxifylline (oxpentifylline), desferrioxamine, anti-TNF antibody, cyclosporin and hyperimmune serum. Unfortunately none has proved to be beneficial, indeed about half (for example dexamethasone, heparin, anti-TNF antibody, desferrioxamine, and the prophylactic phenobarbitone mentioned above) were apparently harmful in trials. None of these adjuvants should be used. Paracetamol and antibiotics are safe. Dopamine is also safe (although there is no evidence that it improves renal function), whereas adrenaline (epinephrine) provokes lactic acidosis, and is best avoided if inotrope support is required.

Exchange transfusion

There have been no randomised trials of exchange transfusion in malaria, but a series of anecdotal reports and uncontrolled series all suggest that it is beneficial in very seriously ill patients. If exchange does work, then it is probably by removing rigid *uninfected* red cells and replacing them by more deformable cells, and much less by removing the cells containing malaria parasites (after all the antimalarial drugs do that rapidly). So should exchange transfusion be done? If antimalarial drug treatment, haemofiltration and ventilation (if necessary) are all under way, there is cross-matched blood, experienced medical personnel, adequate monitoring and suitable facilities readily available then yes – but if these are not available, the risks of the procedure may well outweigh the benefits. There is no consensus opinion. Partial exchange (2–3 L in an adult) may well be sufficient.

DELAYED COMPLICATIONS AND RESIDUAL SEQUELAE

Most survivors from cerebral malaria make a complete recovery without detectable sequelae. A small proportion of patients (less than 2%) who recover consciousness will lapse again into coma. This may be associated with raised protein and lymphocytes in the CSF, suggesting an immunological pathogenesis distinct from that causing cerebral malaria itself. This usually recovers. Self-limiting psychosis or behavioural change may also follow cerebral malaria. Encephalopathy or psychosis are significantly associated with the use of mefloquine as oral maintenance treatment (5% of all cases), so clearly, in such cases, there is an iatrogenic component (Mai *et al*. 1996). Mefloquine should not be used following cerebral malaria. Occasional patients develop tremor, extrapyramidal abnormalities, or cerebellar ataxia following cerebral malaria. These usually resolve spontaneously.

Persistent detectable neurological sequelae are found in less than 3% of adults who recover from cerebral malaria but in a higher proportion of children. Approximately 11% of children have evidence of significant residual abnormalities, although these are often stroke or cortical blindness, indicative of large vessel territory ischaemia. Why a microvascular pathology leads to residual macrovascular territory abnormalities is not clear. Of the children with residual abnormalities, approximately half make a full recovery, 25% some recovery and 25% are permanently disabled. More subtle learning and

© 2004 Blackwell Publishing Ltd

Pract Neurol: first published as 10.1111/j.1474-7766.2004.05-199.x on 1 February 2004. Downloaded from http://pn.bmj.com/ on January 21, 2022 by guest. Protected by copyright.

educational disabilities are more common than has previously been appreciated (Holding & Snow 2001). For such a common disease in tropical countries, this results in a significant burden on impoverished societies.

CONCLUSIONS

- Any patient with fever and altered mental status who lives in or has travelled from a malaria endemic area must have thick and thin blood films examined for malaria parasites.
- Coma + malaria parasitaemia = cerebral malaria (until proved otherwise).
- In malaria endemic areas, cerebral malaria is mainly a disease of children, whereas in areas of low malaria transmission and in travellers it occurs mainly in adults.
- Children recover more rapidly than adults.
- Cerebral malaria is a multisystem disease requiring intensive care management.
- Deep coma, with metabolic acidosis, hypoglycaemia, and renal impairment indicate a poor prognosis.
- Antimalarial treatment (quinine, artesunate, artemether, or if these are unavailable – quinidine) must be started immediately with an initial loading dose. The initial dose should be reduced only if there is a convincing history of adequate antimalarial treatment before admission to hospital.
- Convulsions are common, particularly in children, but prophylactic phenobarbitone may cause respiratory arrest. Patients requiring repeated anticonvulsants should be intubated swiftly by an experienced operator and ventilated.
- Haemofiltration or dialysis should be started early in patients with acute renal failure or severe metabolic acidosis.
- Sudden unexplained deterioration may result from hypoglycaemia or sepsis.
- Mefloquine should not be given following cerebral malaria.
- Residual neurological sequelae occur in 11% of children but < 3% of adults.

ACKNOWLEDGEMENTS

I am very grateful to colleagues in Thailand, Vietnam, The Gambia and Kenya who contributed most of the clinical research described. I am a Wellcome Trust Principal Fellow. This article was reviewed by Jeremy Farrar, Vietnam

REFERENCES

Marchiafava E & Bignami A (1894) *On Summer-Autumnal Fever*. London: New Sydenham Society.

Crawley J, Waruiru C, Mithwani S *et al.* (2000) Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. *Lancet*, **355**, 701–6.

Senanayake N (1987) Delayed cerebellar ataxia: a new complication of falciparum malaria. *British Medical Journal*, **294**, 1253–4.

Day NP, Phu NH, Mai NT *et al.* (2000) The pathophysiologic and prognostic significance of acidosis in severe adult malaria. *Critical Care Medicine*, **28**, 1833–40.

English M, Muambi B, Mithwani S & Marsh K (1997) Lactic acidosis and oxygen debt in African children with severe anaemia. *Quarterly Journal of Medicine*, **90**, 563–9.

Holding PA & Snow RW (2001) Impact of *Plasmodium falciparum* malaria on performance and learning: review of the evidence. *American Journal of Tropical Medicine and Hygiene*, **64**, 68–75.

Lewallen S, Harding SP, Ajewole J *et al.* (1999) A review of the spectrum of clinical fundus findings in *P falciparum* malaria in African children with a proposed classification and grading. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **93**, 619–22.

Looareesuwan S, Wilairatana P, Krishna S *et al.* (1995) Magnetic resonance imaging of the brain in cerebral malaria. *Clinical Infectious Diseases*, **21**, 300–9.

Mai NTH, Day NPJ, Chuong LV *et al.* (1996) Post–malaria neurological syndrome. *Lancet*, **348**, 917–21.

Medana IM, Day NP, Hien TT *et al.* (2002) Axonal injury in cerebral malaria. *American Journal of Pathology*, **160**, 655–66.

Newton CR, Hien TT & White NJ (2000) Cerebral malaria. *Journal of Neurology, Neurosurgery and Psychiatry*, **69**, 433–41.

Newton CR & Krishna S (1998) Severe falciparum malaria in children: current understanding of pathophysiology and supportive treatment. *Pharmacological Therapy*, **79**, 1–53.

Newton CR, Peshu N, Kendall B *et al.* (1994) Brain swelling and ischaemia in Kenyans with cerebral malaria. *Archives of Disease in Childhood*, **70**, 281–7.

Phu NH, Hien TT, Mai NTH *et al.* (2002) Hemofiltration and peritoneal dialysis in infection associated acute renal failure in Vietnam. *New England Journal of Medicine*, **347**, 895–902.

Silamut K, Phu NH, Whitty C *et al.* (1999) A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain. *American Journal of Pathology*, **155**, 395–410.

The Artemether-Quinine Meta-analysis Study Group. (2001) A meta-analysis using individual patient data of trials comparing artemether with quinine in the treatment of severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **95**, 637–50

White NJ (1991) Lumbar puncture in cerebral malaria. *Lancet*, **338**, 640–1.

White NJ, Warrell DA, Chanthavanich P *et al.* (1983) Severe hypoglycaemia and hyperinsulinaemia in falciparum malaria. *New England Journal of Medicine*, **309**, 61–6.

World Health Organization. (2000) Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **94**, S1–90.

© 2004 Blackwell Publishing Ltd

Pract Neurol: first published as 10.1111/j.1474-7766.2004.05-199.x on 1 February 2004. Downloaded from http://pn.bmj.com/ on January 21, 2022 by guest. Protected by copyright.