Severe malaria

Severe malaria develops when partial immunity is not present.

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Pathogenesis

Infection with *Plasmodium falciparum* induces changes in red blood cells that cause them to adhere to each other and to the endothelium. These changes in the red cells reduce their deformability. Red cells become sequestered in the microcirculation (Fig. 1) where maturation of the parasite occurs prior to haemolysis and infection of new red blood cells. Blockage of the microcirculation by sequestered red cells may result in organ dysfunction and failure, which is responsible for most of the manifestations of severe malaria. Pro-inflammatory cytokines, notably TNF-α, also play an important role in the pathogenesis of severe malaria. Red cell sequestration does not occur with the other plasmodium species and, apart from extremely rare cases, they do not cause severe malaria or death.

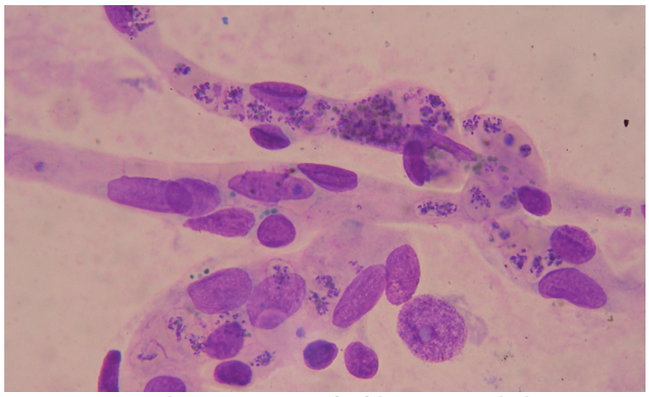

Fig. 1. Microvascular sequestration of P. falciparum *in the human brain. (Photo by Kamolrat Silamut, Wellcome Mahidol University Oxford Tropical Medicine Programme – with permission.)*

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Epidemiology

In endemic areas with malaria transmission throughout the year partial immunity develops. This protects individuals from severe malaria. Severe malaria only occurs when this immunity has not yet developed (infants and young children), or is impaired (e.g. primigravidae, HIV infection), or is lost (adults re-exposed to malaria after 2 - 3 years in a non-malarial area). Young children in particular are at risk of severe malaria.

Immunity does not exist in travellers from non-malarial areas, and does not develop in people who live in areas where malaria is seasonal, such as in South Africa. Therefore these individuals are all at increased risk of severe malaria.

A critically important point in assessing patients with suspected severe malaria is the malaria immune status of the individual.

Clinical features

Falciparum malaria can progress rapidly from initial symptoms to the development of severe malaria. In adults this progression occurs over a few days, but in infants and young children it may occur within a day.

A critically important point in assessing patients with suspected severe malaria is the malaria immune status of the individual. Individuals who might have partial immunity (i.e. they have grown up in areas with malaria transmission throughout the year) could have asymptomatic parasitaemia with *P. falciparum* and their presenting illness may be due to another cause (e.g. meningococcal meningitis in an older child with possible cerebral malaria). It is therefore particularly important to exclude other causes in partially immune patients. In patients without malaria immunity asymptomatic parasitaemia does not occur, so the diagnosis of malaria is established if parasitaemia is present.

A variety of case definitions have been developed for severe malaria. It is important to recognise that these case definitions are primarily for researchers working in areas with malaria transmission throughout the year. If a patient is judged to be severely ill in ways not listed in Table I, the patient should be treated for severe malaria (by giving antimalarials parenterally rather than orally – see below). Parenteral treatment must also be given if the patient is vomiting, which is common in malaria.

Cerebral malaria is more common in children. This presents with decreased level of consciousness, seizures or non-localising neurological signs. Retinopathy, consisting of haemorrhages, Roth spots or segmental whitening of blood vessels, is frequently present in severe malaria. A classic presentation of severe malaria is discoloured urine due to haemoglobinuria from severe intravascular haemolysis: 'blackwater fever'.

Management

Resuscitative and general support measures are critically important in severe malaria. One caveat though is that one should be cautious about excessive fluid administration as this can lead to worsening or unmasking of the adult respiratory distress syndrome, which is not uncommon in severe malaria. Ideally fluids should be administered with monitoring of central venous pressure. Airway management is critically important in cerebral malaria. Blood, platelets and clotting factors may be necessary.

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Haemofiltration or dialysis should be instituted in patients with rapidly increasing creatinine or with other criteria for renal replacement therapy.

Patients should always be treated in the highest available level of care – ideally in an intensive care unit. If the patient is to be transferred to another facility it is essential to administer an effective parenteral antimalarial and provide appropriate resuscitation prior to transfer.

Antimalarial treatment should be commenced urgently with a loading dose (20 mg/kg by slow infusion) of quinine. The maintenance dose of quinine is 10 mg/kg. Quinine must be given by slow intravenous infusion as it is cardiotoxic and bolus doses may cause hypotension or arrhythmias.

In severe malaria it is essential to give a loading dose of quinine to ensure that therapeutic levels of free quinine are reached as soon as possible, as the free drug is the active drug. Quinine binds to a protein (α_1-acid glycoprotein), which is an acute phase reactant (therefore higher concentrations of this protein occur in severe malaria). Protein binding is also stronger in severe malaria.

Quinine causes insulin release from the pancreas and may cause hypoglycaemia in about 2 - 3% of patients. It is essential to frequently monitor glucose, particularly in patients with cerebral malaria as the symptoms and signs of hypoglycaemia will be absent. Despite its toxicity, serious adverse drug reactions are uncommon with quinine.

The dose of quinine should be reduced by a third in patients with renal impairment only after the first 48 hours.

Oral quinine should be given when the patient is well enough to complete a 7-day course, together with 7 days of doxycycline (or clindamycin for young children and pregnant women).

Artemisinin derivatives are a new class of antimalarials that are more rapidly acting than the older agents. Intravenous artesunate has been shown to reduce mortality by about a third when compared with intravenous quinine for severe malaria in randomised controlled trials, but artesunate is not yet available in South Africa.

Broad-spectrum antibiotics should routinely be given to all patients with severe malaria as concomitant bacteraemia may occur, especially in children. Exchange transfusion is often advocated in severe malaria, particularly when there is heavy parasitaemia. However, exchange transfusion does not get rid of sequestered red cells, which are responsible for many of the manifestations of severe malaria. Replacing red cells that have reduced pliability as a consequence of *P. falciparum* infection may result in improvement, but there is no convincing evidence that this is the case. Exchange transfusion is expensive, time-consuming and not without risk. Therefore exchange transfusion cannot be recommended. Several adjunctive therapies have been evaluated in severe malaria, but these have not shown benefit or have caused harm (e.g. corticosteroids, heparin).

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Table I. Simplified case definition of severe malaria*

Decreased level of consciousness
Prostration (in children)[+]
Shock
Acidosis
Severe anaemia (haematocrit <20%)
Visible jaundice
Renal impairment
Parasitaemia >10% of red cells
Hypoglycaemia (not induced by quinine)
Respiratory distress

* Adapted from: South East Asian Quinine Artesunate Malaria Trial. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* 2005; 366: 717-725.

[+] Defined as the inability to sit upright in a child normally able to do so, or to drink in the case of children too young to sit.

Prognosis

The mortality of severe malaria is about 25% with quinine therapy, and this varies considerably with the time taken to reach parenteral treatment and the level of care accessed. Cerebral malaria, respiratory distress and severe anaemia are associated with the worst prognosis. Neurological recovery after cerebral malaria occurs in the majority, but may be delayed.

Recommended reading

WHO. Severe falciparum malaria. *Trans Roy Soc Trop Med Hyg* 2000; Suppl 1.

Jones KL, Donegan S, Lalloo DG. Artesunate versus quinine for treating severe malaria. *Cochrane Database Syst Rev* 2007, Issue 4. Art. No.: CD005967. DOI: 10.1002/14651858.CD005967.pub2.

In a nutshell

- Sequestration of red cells in the microcirculation is the key to the pathogenesis of severe malaria.
- The malaria immune status of the individual is important in determining the risk of developing severe malaria and in the clinical assessment of possible severe malaria.
- General supportive measures and resuscitation are critically important, but beware of over-hydration.
- Parenteral antimalarial treatment with quinine, with a loading dose, must be given in all cases of severe malaria.
- Parenteral artesunate is a better treatment for severe malaria (mortality is about a third lower), but this is not yet available in South Africa.
- Case definitions of severe malaria are helpful, but clinicians should also implement parenteral antimalarial treatment if they are concerned about any patient, even if the case definitions are not fulfilled.