

Classic acute uncomplicated attack

Most clinical episodes of malaria are characterized by fever with aspecific symptoms. Certainly, in children the presentation can be very misleading. Any fever should bring the possibility of malaria to mind. There is a danger, however, that every fever episode may be regarded as malaria and other important diagnoses are then likely to be missed.

P. falciparum: typical incubation time: 7 to 30 days. If a person is taking preventive antimalarials and if the parasite is partially resistant, there may be temporary suppression of a malaria attack. The fever is generally irregular. If the attack is not treated, after a few weeks a regular fever pattern will develop with peaks every 2 days (tertian malaria, so called because the fever reappears on the third day, reckoning the day of the paroxysm as the first. This is rare in everyday clinical practice). At the beginning of the attack the symptoms are similar to influenza: general malaise, tiredness, muscle pain, headache but in general without respiratory tract problems or running nose. These symptoms are non-specific. After a while the muscle pain and headache become worse. Sometimes there is also abdominal pain and diarrhoea. Rarely there is a classic attack: this lasts for approximately 12 hours and occurs every 48 hours. At first cold shivers with high fever occur, followed by an intense feeling of heat and fever, leading to a sweating stage with a drop in fever. Most *falciparum* attacks do not follow this classic pattern. Therefore what is referred to as a classic attack is paradoxically not the general rule.

P. vivax and *P. ovale*: the incubation time is a few weeks to years. The awakening of dormant parasites in the liver (hypnozoites) explains the potential for late relapses. The fever is sometimes regular (every 48 hours) especially in cases of recrudescence (tertian malaria). In 1922 *P. vivax* was introduced for the treatment of neurosyphilis. It was thought that the bacterium which causes syphilis had little resistance to heat, so the high fever would kill the bacteria (*Treponema pallidum*).

P. malariae: the incubation time is 3 weeks to many years. The very late attacks are probably not due to awakened hypnozoites (to date these have never been detected) but due to the activation of blood parasites which are present at a very low concentration. Fever peaks may occur every 72 hours (quartan malaria).

P. knowlesi is a monkey parasite which can be misidentified as *P. falciparum* in the early ring stage and as *P. malariae* in the older stages. It has the shortest asexual life cycle of all i.e. 24h. The prepatent period is 9-12 days. At present, no hypnozoites have been found. PCR is needed to firmly identify this species.

Mixed infections: mixed infections do occur, but for reasons which are unclear they are much less common than would be expected based on the prevalence of the individual species. Underreporting may play a part, but this is probably a real phenomenon (partial cross-immunity to heterologous species? biological interference?).

Natural course of malaria in the autochthonous population

Children are very susceptible to infection. The highest mortality is found in children below the age of 5 years. Gradually, after repeated infections, a partial immunity develops in those who survive. There is a high degree of tolerance to the infection in adults, provided they live in a stable malaria region. This semi-immunity (or “premunition”) is maintained by repeated infections and mild latent infections. It disappears after approximately 6 to 24 months if there is no further infection (e.g. a stay in a non-malaria region).

This partial immunity is reduced during pregnancy. A pregnant woman is at increased risk of hypoglycaemia and cerebral malaria. Malaria is an important cause of severe (sometimes spectacular) anaemia in the mother, low birth weight, premature birth, abortion and increased perinatal death. Chondroitin sulphate and hyaluronic acid, both present in abundance around the syncytiotrophoblasts of the placenta, are mucopolysaccharides (glycosamine glycanes) which act as receptors for red blood cells infected with *P. falciparum*. Probably there are also other receptor molecules. Infected cells accumulate in the placenta resulting in reduced placental function.

The placental barrier is very seldom passed. Congenital malaria is not common and occurs chiefly in neonates of non-immune women. Neonates of semi-immune women receive transplacental anti-plasmodium antibodies. Due to this passive resistance in the first 3-6 months they are at a lower risk of malaria.

Several observations of humans infected with both malaria and helminths suggest that co-infection provides a benefit to either parasite. The evidence indicates that malaria patients co-infected with helminths are protected from severe malaria possibly through skewering of the immune response towards T helper (Th)2 immunity.

Malaria and HIV interact in several, rather complex ways. The CD4+ lymphocytes play a central role in the defence against malaria and their characteristic decrease during the course of HIV infection explains why severely immunosuppressed HIV-positive individuals are so susceptible to severe malaria. In malaria-endemic regions, severe malaria may be considered as an “opportunistic infection” and any diagnosis of complicated malaria in adults should trigger HIV testing.

Acute severe malaria

Acute severe falciparum malaria is a medical emergency. This encompasses:

- Coma: repeated generalized convulsions
- Hypoglycaemia: reduced consciousness, aggressive behaviour
- Severe anaemia: weakness, tachypnoea, pale mucosae
- Tendency to spontaneous bleeding (pronounced thrombocytopenia)
- Circulatory collapse (shock); cfr. below “algid malaria”
- Pulmonary oedema (dyspnoea and bilateral crackles) leading to acute respiratory distress syndrome (ARDS)
- Haemoglobinuria (dark urine)
- Kidney failure: urinary output should be monitored (but attempts to force urine production may cause circulatory overload!)
- Acidosis (chiefly due to lactic acid): tachypnoea. If too many salicylates are given this may exacerbate acidosis (not unusual in febrile patients).
- Other important signs are: marked jaundice, confusion without coma, extreme generalized weakness or prostration (child cannot remain sit and don't want to eat/drink).

The priorities are cerebral involvement, severe anaemia, hypoglycaemia, and the presence of hyperparasitaemia. The degree of parasitaemia correlates with the severity of the symptoms: the higher the parasitaemia, the greater the risk of severe symptoms. It should be borne in

mind that the parasitaemia (the percentage of parasitized cells that are found in a smear preparation) changes by the hour. This is because the red blood cells with mature *P. falciparum* parasites (schizonts) attach themselves to the small capillaries of deep organs therefore are not found in a thin blood smear. A parasitaemia of 0.5% is already severe, 2% is pronounced, and patients with a parasitaemia of more than 10% have a relatively poor prognosis. Over 25% is often fatal. Another consideration is that a parasitaemia of 3% in someone who still has a normal red blood cell count, is different from a parasitaemia of 3% in an anaemic patient.

Hypoglycaemia may quickly lead to general deterioration and coma. It is common in children (up to 25% of cases) and pregnant women. Glucose may be life-saving. If the glycogen store in the liver is low (i.e due to malnutrition) the risk of hypoglycaemia increases [glycogen is converted to glucose]. The conversion of glycogen to glucose is also inhibited by certain cytokines which are released during infection with *P. falciparum* [Hypoglycaemic effects of TNF- α and possibly interleukin-1 and TNF- β]. The parasites themselves also use glucose for their metabolism and contribute to the hypoglycaemia if they are present in large numbers. Quinine can stimulate the secretion of insulin from the pancreas and in this way can also contribute to hypoglycaemia.

The term “**algid malaria**” (L. “*algidus*” = cold) is obsolete. The condition is characterized by hypotension with progression to shock. The patient is clammy and often feels cold. There is no fever. Often there is concurrent septicaemia with Gram-negative bacteria. Mortality is high. Therapy with artesunate or quinine, treatment with antibiotics and (cautious, see ARDS) IV fluid administration is of great importance. Shock seldom occurs in malaria if there is no septicaemia. However splenic rupture can also cause hypovolemic shock.

Splenic rupture. This may occur spontaneously or after an unobserved trauma. This complication can occur in *P. falciparum*, *P. vivax*, *P. ovale* or *P. malariae*. The presence of intraperitoneal fluid is suggestive in this context. In these cases ultrasound can often detect a splenic hematoma, splenic rupture or intraperitoneal fluid. A diagnostic peritoneal lavage may be indicated.

Cerebral malaria is the main cause of death (80 %) in falciparum malaria. This complication occurs chiefly in non-immune persons (children, travellers). Cerebral signs include confused

behaviour, psychosis, convulsions, stupor, coma, paralysis. Unlike meningitis, there is no real neck stiffness (pain) or photophobia (intolerance to light) but neck retraction and opisthotonos (neck muscle spasm) may occur. Sometimes the difference between neck stiffness and neck retraction is not clinically clear. It is typical of the coma that it develops swiftly in 75% of cases and quickly disappears. If a child survives cerebral malaria it has approximately a 10% chance of significant long term sequelae. Children with cerebral malaria and with a normal eye fundus have a good prognosis, while papilledema and retinal bleeding suggest a guarded prognosis. Malarial retinopathy is increasingly considered as a specific diagnostic criteria of cerebral malaria, but sensitivity of this abnormality is rather poor (meaning that its absence does not exclude cerebral involvement). Repeated generalized convulsions should not be regarded as “normal” febrile convulsions. Severe convulsions with contraction of the abdominal muscles and compression of the stomach, may cause reflux of gastric acid and food into the pharynx. Aspiration of gastric contents into the lungs is a real danger as this may result in Mendelson’s syndrome (chemical pneumonitis) or aspiration pneumonia. If there are convulsions, these are stopped by administering diazepam (Valium®) IV. A CT scan or MRI scan of the brain of patients with cerebral malaria shows few abnormalities except an occasional increase in cerebral volume. Herniation of the brain stem is a rare event.

If confronted by a febrile coma or confusion with fever in the tropics, glucose must be administered (preferably IV), artemisinin (or quinine if artemisinin unavailable) therapy should be instituted and a lumbar puncture carried out without hesitation (to rule out meningitis). Of the persons who die in hospital due to cerebral malaria, 50% of the fatalities occur within the first 12 hours after admission. At autopsy countless petechiae can be seen in the brain. Small ring-shaped haemorrhages also occur around cerebral blood vessels.

Febrile convulsions

Febrile convulsions are generalized tonic-clonic convulsions. They only occur in children between the age of 6 months and 5 years and will not be repeated during the same fever episode. They occur during the phase in which the fever is rising fast. They always last less than 15 minutes, but post-ictal coma can take up to 1 hour. There is never postictal hemiparesis. It is important to differentiate between febrile convulsions and convulsions

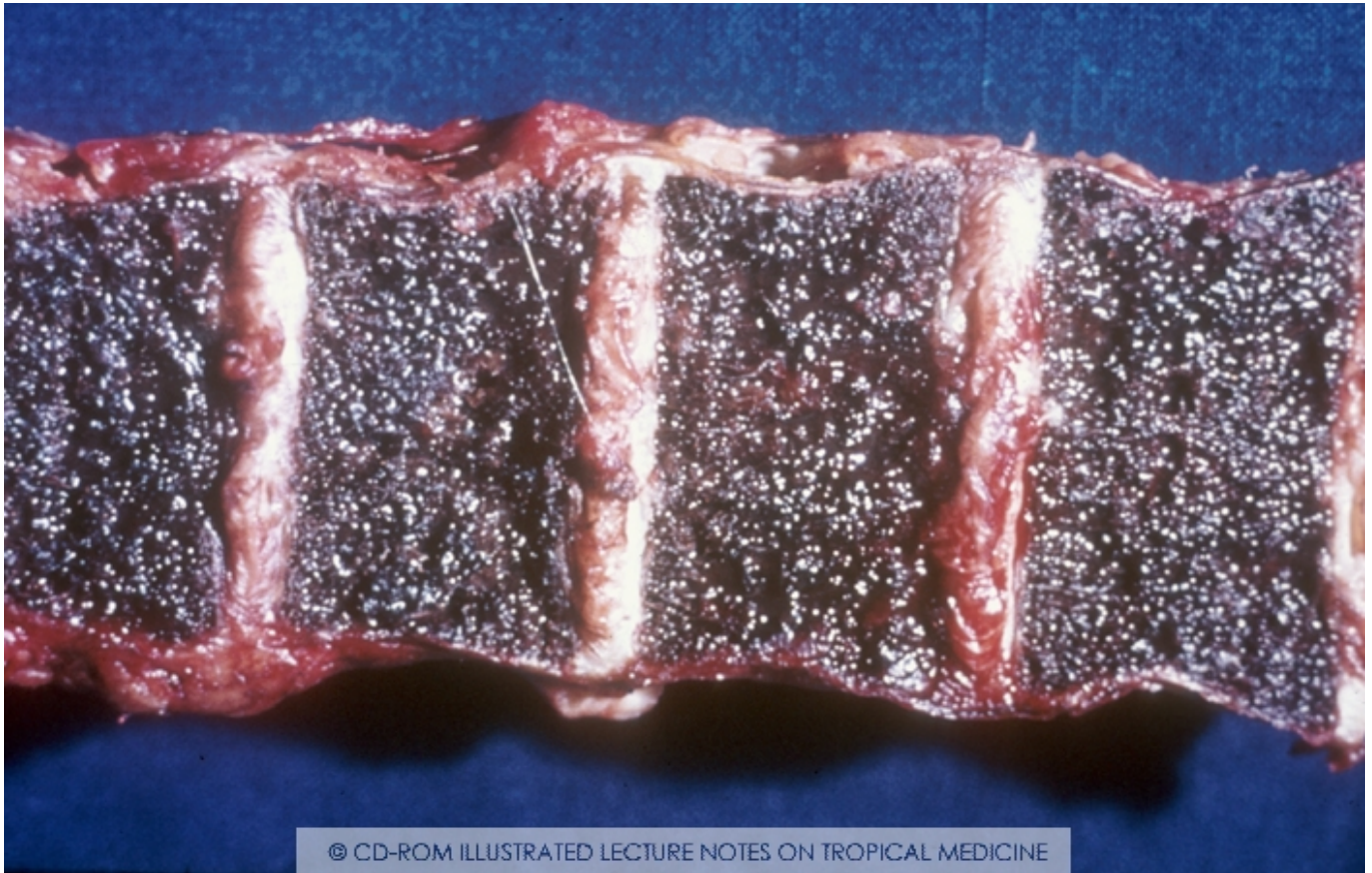
during fever (e.g. cerebral malaria, meningitis, cerebral abscess). Approximately 2% of children have a tendency (possibly genetic) for febrile convulsions. The risk that epilepsy will develop in this group of patients is no greater than in children without febrile convulsions. Brief and sporadic attacks have a good prognosis. No maintenance therapy with anti-epileptic agents is required.

Severe anaemia occurs due to haemolysis (of both parasitized and non-parasitized red blood cells – the latter via immune-mediated mechanisms), due to excessive action of the spleen i.e. hypersplenism (until weeks after the infection), due to possible haemorrhages (low blood platelets, splenic rupture) and due to disturbed production of new blood cells in the bone marrow (dyserythropoiesis) due to TNF-alpha.

Hyperpyrexia (very high fever above 40°C) should be treated by cooling the patient and administering paracetamol. It is assumed that malaria fever is caused when lysis of the red blood cells releases malaria pigment (hemozoin) as well as GPI-anchors (“malaria toxin”) which are absorbed by the reticulo-endothelial system. This in turn releases endogenous pyrogens (cytokine network). The concentration of tumour necrosis factor in the peripheral blood correlates with the severity of the malaria. In cases of repeated malaria attacks the liver, spleen and bone marrow are stained black by the enormous amounts of hemozoin. Hyperpyrexia is no longer considered as a criteria of severity (WHO classification of 2000).

Black water fever

Black water fever is a severe life-threatening complication. Acute massive haemolysis occurs through immuno-allergic mechanisms which are not fully understood. It has been observed after taking halofantrine, artemisinin-derivatives and after irregular use of quinine. The parasitaemia is generally very low. There is high fever, jaundice, back pain, shock and very dark urine. Renal insufficiency occurs: the urine production is very low (oliguria) or zero (anuria). Mortality is very high. When quinine was no longer used prophylactically, black water fever became very rare. Differential diagnosis should be made with severe malaria itself, leptospirosis and viral haemorrhagic fever.



Black pigmentation of the bone marrow in the spine, due to accumulation of malaria pigment (repeated malaria). Photo Dr Gigase. Copyright ITM

Acute renal failure may also be caused by shock, hypovolemia with reduced renal circulation, disseminated intravascular coagulation (DIC), obstruction of the renal glomeruli by parasitized red blood cells and by the precipitation of released haemoglobin in the kidney (pigment nephropathy). The combination of these factors can result in acute tubular necrosis. Glomerulonephritis may occur in chronic *P. malariae* malaria (cfr. infra), but this complication plays no part in acute renal problems.

Pulmonary oedema is a common complication of severe malaria. The dividing line between overhydration and dehydration is narrow. Adults easily develop non-cardiogenic pulmonary oedema if there is excessive fluid overload, but on the other hand dehydration and hypovolemia may lead to hypotension, shock and renal failure. Pneumonia is observed quite often if coma lasts for longer than 3 days. ARDS (acute respiratory distress syndrome) may

occur. This is caused by diffuse damage to the vascular endothelium and the alveolar epithelium. There is a rapid progression towards dyspnoea, arterial hypoxia, bilateral patchy pulmonary infiltrates due to pulmonary oedema with a protein-rich fluid. The treatment is both etiological and symptomatic: mechanical ventilation, with or without intubation or an endotracheal cannula, possibly with NO (nitrogen monoxide), high-dosed oxygen and positive end-expiratory pressure (PEEP).

Chronic falciparum malaria

Where *P. falciparum* is partially resistant to the therapeutic drug locally used (e.g. chloroquine), the parasite may be suppressed, but will remain present (not completely cleared). This may lead to a whole range of clinical pictures, from asymptomatic parasitaemia through to mild unspecific symptoms, to significant chronic malaise, anaemia and fatigue. Curative therapy with atovaquone/proguanil or artemisinin-based combination therapy (ACT, see below), for example, produces rapid improvement.

Hyperreactive malaria splenomegaly (HMS)

Some adults have a very strong immunological reaction to *P. falciparum* antigens. The level of IgM in the blood is very high. Due to the polyclonal immune stimulation, all kinds of autoantibodies can appear. Immune complexes are formed, and are removed by the reticulo-endothelial system, which leads to splenomegaly and sometimes hepatomegaly. In these individuals the swollen spleen swells also breaks down normal, non-parasitized red blood cells. The number of parasites is very low, but very high concentrations of anti-*P. falciparum* antibodies can be detected. The splenomegaly disappears after curative therapy with, e.g. ACT followed by months or even years of adequate malaria chemoprophylaxis (if persistent exposure in a malaria region), but recovery is very slow. In rare cases splenectomy is necessary. Steroids have no place in the treatment.

HMS and splenic lymphoma

HMS may be very similar to a certain indolent splenic lymphoma (e.g. splenic lymphoma with villous lymphocytes). The latter disorder is related to B-cell chronic lymphocytic leukaemia and occurs chiefly in elderly persons. The disease is often accompanied by

significant cytogenetic abnormalities and monoclonal “villous” B-lymphocytes in the peripheral blood. It is likely that in HMS, excessive stimulation of the B-lymphocytes by malaria antigens increases the risk that oncogenic mutation may occur, followed by clonal growth of these cells.

Burkitt's lymphoma

This malignant tumour originates from B-lymphocytes. It is very aggressive with a volume doubling time of about 3 days. The endemic form occurs in sub-Saharan Africa and is also found in Papua New Guinea. In these areas, it accounts for up to 50% of childhood tumours.

One hypothesis states that repeated malaria attacks may have a mitogenic effect on infected B-lymphocytes (polyclonal B-cell stimulation) increasing the risk of mistakes during chromosomal replication which subsequently would lead to neoplastic behaviour.

Burkitt's lymphoma generally presents with swelling of the jaw and mouth ulcerations (75%, especially maxilla tumours), abdominal swelling with ascites (60%) and central nervous system involvement (30%, including cranial nerve palsies, malignant pleocytosis or paraplegia). Infection with the Epstein-Barr virus (cf. mononucleosis) plays an important part in the endemic form of Burkitt's lymphoma, probably by causing genetic instability. Epstein-Barr viral DNA is found in about 90% of African Burkitt's lymphomas.

The tumour responds well to cytostatic drugs. The alkylating agent cyclophosphamide (Endoxan®) is first choice (the target dose 1-1.5 gram/m² IV every 3-4 weeks with 2 doses in remission), but more complex chemotherapies (methotrexate, vincristine, CHOP-R, hyper-CVAD,...) are difficult to evaluate in low-resource settings. About 80% of patients can achieve complete tumour regression and 10% have a partial response. About 50% will relapse.



Nephrotic syndrome secondary to chronic infection with *Plasmodium malariae*. Notice the swollen face and ascites. Photo prof. Gigase. Copyright ITM



Burkitt's lymphoma in a Cambodian woman, aspect before chemotherapy. Photo Dr Lut Lynen, copyright ITM

Nephrotic syndrome in *P. malariae*

Chronic infection with *P. malariae* may, via immunological mechanisms (chronic immune complex glomerulonephritis) cause a nephrotic syndrome, characterized by oedema and proteinuria (more than 3.5 gram per 24 hours). There is often significant hyperlipidaemia and lipid bodies are sometimes found in the urine.

If a kidney biopsy is carried out, it should be borne in mind that severe bleeding will occur in 1% of cases. The treatment of nephrotic syndrome is difficult. Curative malaria treatment is of course indicated but will not produce improvement of the kidney function. Salt restriction

and diuretics are indicated (both thiazide and loop diuretics). Treatment with an ACE-inhibitor [angiotensin-converting enzyme-inhibitor such as enalapril] should be ideally initiated in settings where it is available. Steroids and immunosuppressive agents are of little benefit in this disorder. An important challenge is to distinguish the entity from minimal change glomerulonephritis (electron microscopy needed to confirm “minimal change” on biopsy specimen).