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Malaria and acute renal failure

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Of the four human malaria parasites, only *Plasmodium falciparum* causes acute renal failure (ARF), though *Plasmodium malariae* can cause a chronic nephropathy leading to nephrotic syndrome and eventual chronic renal failure. In areas of the tropical world where *P falciparum* is endemic and its transmission stable, severe malaria affects mainly children; it is manifested as either coma (cerebral malaria) or severe anaemia and claims more than a million young African lives a year. Surviving children in these populations gradually develop a degree of immunity to falciparum malaria. Adults are infected frequently by the parasite but rarely develop severe disease. Although hypoglycaemia and lactic acidosis are common findings in African children with severe malaria, multi-organ failure involving the kidneys or the liver is extremely rare. However, in areas of the world where transmission of falciparum malaria is unstable and the risk of infection low, or when non-immune individuals visit any area where falciparum malaria is endemic, severe malaria may occur at any age. In this setting, severe malaria frequently takes the form of a multi-system disorder, variably causing ARF, jaundice, coma, lactic acidosis, hypoglycaemia, anaemia, pulmonary oedema and haemodynamic shock. Hence, ARF is a common finding among cases of 'imported' severe malaria seen in hospitals in the Northern hemisphere, and its diagnosis and treatment are important components of the management of such cases.

In a recent study of 560 cases of severe adult malaria in Vietnam[1], 28% of patients had renal failure (defined as plasma creatinine ≥264 μmol/l (3 mg/dl)) on admission, and

Key Points

- ARF is a feature of severe falciparum malaria in non-immune individuals. It is commoner in adults but can occur in children
- Clinically, ARF in severe malaria takes the form of ATN, though it may be non-oliguric in the less acute form
- Volume repletion should be carried out with care, as malaria patients may develop pulmonary oedema at mildly raised or even normal filling pressures. Measurement of central pressures is mandatory
- Treatment with haemofiltration or dialysis should be early, as patients with severe malaria are hypercatabolic and non-renal causes of acidosis (lactic acidosis) frequently co-exist
- Blackwater fever, once much feared, is now rarely associated with dialysis-requiring renal failure

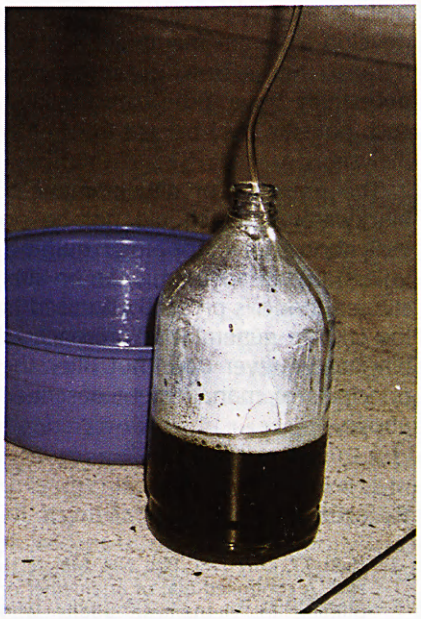
41% had renal failure at some stage during their illness. Overall, 14% required dialysis. Renal failure on admission (oliguric or non-oliguric) was associated with increased mortality (29% in those with renal failure, 9.2% in those without: relative risk, 2.4). Malaria-associated ARF requiring dialysis is less common in Vietnamese children than in adults from the same population, occurring in 5% of cases of childhood severe malaria (DB Bethell; personal communication). This is a significantly higher rate than in African children, where any renal dysfunction is usually subclinical and the need for dialysis vanishingly rare[2].

Clinical features

ARF in severe malaria may present acutely as part of a fulminant multisystem disorder, or develop over several days in patients recovering from the initial acute phase of severe disease. Patients developing renal failure acutely, tend to be oliguric or anuric, frequently have evidence of other vital organ dysfunction including coma, jaundice and co-existing lactic acidosis, and usually require immediate or early dialysis. Haemodynamic shock, pulmonary oedema and rapidly worsening lactic acidosis are frequent pre-terminal features.

Patients developing renal failure after the acute phase of the disease are more likely to have non-oliguric renal failure and less likely to require dialysis. If dialysis is required in this group, the indication is more likely to be uraemic symptomatology or (non-lactic) acidosis than hyperkalaemia or fluid overload.

In general, the clinical presentation of ARF in severe malaria is closer to that of sepsis-related acute tubular necrosis (ATN) than of acute glomerulonephritis: hypertension and oedema do not occur and, although there may be mild proteinuria, the urinary sediment is usually unremarkable apart from occasional leukocytes and granular casts. A polyuric phase frequently follows oliguria, usually preceding an improvement in renal function. Salt depletion and hypokalaemia may occur during this phase. If the patient survives the acute phase of the disease and has no pre-existing kidney disease, rapid recovery of renal function is the norm and dialysis can be discontinued within 2–8 weeks.



'Coca cola' urine from a Vietnamese child with blackwater fever. *Courtesy of Dr Delia Bethell.*

Blackwater fever

Severe cases of this enigmatic condition, comprising fever, massive intravascular haemolysis and haemoglobinuria, can lead to ARF. The precise aetiology is unclear; it occurs only in areas of the tropics endemic for malaria, and is associated with malaria infection, quinine ingestion, and glucose-6-phosphate dehydrogenase deficiency. It is not known how the presence of one or more of these factors leads to haemolysis, and no single factor can explain all cases of blackwater fever. Once a major cause of renal failure and malaria-associated mortality, it is now relatively uncommon and rarely leads to severe ARF. In a recent series of 50 cases of blackwater fever, only three patients required dialysis and only one died[3].

Pathophysiology

The clinical features of malaria-associated ARF are very similar to those of the ATN syndrome seen in patients with bacterial sepsis or hypovolaemia, suggesting that the pathological processes may also be similar. In support of this view, the few renal biopsies taken in malaria-associated ARF have tended to show pathological changes in the tubules consistent with ATN[4,5], and reports of glomerulonephritis are very rare[6]. Invasive studies of renal haemodynamics and oxygen transport have demonstrated reduced renal blood flow and renal oxygen delivery in malaria[7], and angiographic studies in two malaria patients have shown renal cortical vasoconstriction[8]. It is unclear whether these changes are caused by parasitised erythrocytes sequestered in the kidney causing local microvascular obstruction, or by alterations of intrarenal microvascular flow secondary to the local or systemic release of vasoactive compounds such as cytokines or endothelin.

Renal biopsies from cases of blackwater fever have demonstrated haemoglobin tubular casts and tubular atrophy[9]. The possibility of cast obstruction together with the known toxic effects of haemoglobin on renal tubules make it surprising that ARF with blackwater fever is not more common.

Treatment

Management of malaria-associated ARF is similar to that of severe sepsis-associated ARF. Patients with severe malaria are often dehydrated on presentation, but volume repletion should be undertaken cautiously as pulmonary oedema can develop at relatively low or even normal filling pressures in malaria[10]. Central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) should be monitored (CVP should be $\leq$5 cm H_2O; PAOP $\leq$12 mmHg). Parenteral antimalarial drugs should be given, the choice depending on where the malaria was contracted (eg chloro-

quine resistance) and where the patient is being treated (drug availability)[11]. The use of low ('renal') dose dopamine and frusemide in early or incipient renal failure remains controversial[12]. Haemodynamic shock refractory to volume repletion can be treated with inotropes, though adrenaline should be avoided as it causes lactic acidosis in severe malaria[13].

A retrospective study revealed that malaria-associated ARF mortality was 70% in the absence of dialysis facilities; this was halved to 35% after the introduction of peritoneal dialysis[14]. Although this and other studies demonstrate that peritoneal dialysis is generally effective in malaria-associated ARF[15], our unpublished comparison with pumped veno-venous haemofiltration suggests that haemofiltration may be more effective in terms of correction of acidosis, creatinine and potassium, and may even allow a shorter period of dialysis dependence. Intermittent haemodialysis may also be used[16], though a continuous form of renal replacement therapy is preferable in haemodynamically unstable patients. The standard indications for dialysis apply (metabolic acidosis, hyperkalaemia, fluid overload, and signs or symptoms of uraemia), but in rapid onset disease the threshold for initiating dialysis should be low. Patients with fulminant malaria are hypercatabolic and often develop a severe metabolic acidosis before the serum creatinine or potassium have risen substantially; such patients may benefit from early dialysis.

The presence or development of blackwater fever should not be an indication for stopping quinine, unless a qinghaosu drug can be substituted (none is presently licensed in the UK). In general, the presence of blackwater fever does not alter the principles of management described above.

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