# Acute Falciparum Malaria

## COMPLICATIONS AND TREATMENT

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## SUMMARY

**The life-threatening complications of imported malaria are complex disturbances involving many systems in the body. Prompt antimalarial therapy is essential, but all other treatment has to be tailored individually to each patient's special needs.**


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The treacherous nature of *P. falciparum* malaria cannot be overemphasised, in view of the high frequency with which it commences as an indeterminate, mild, febrile illness with vague generalised aches and pains, lumbar backache with headache, nausea and vomiting and, less often, diarrhoea, being common symptoms. Chills with fever develop as the disease progresses, but the typical tertian paroxysms of *P. vivax* malaria, with its abrupt onset, well-defined rigors, high fever, severe headache, rapid defervescence to normal temperature and sense of well-being between attacks, does not occur. Instead, malaise, generalised myalgia and headache persist, increasing prostration is evident, and delirium and confusion are prominent and prolonged. Even if periodicity occurs the temperature does not return to normal levels, and fever is very frequently irregularly intermittent or continuous and may be trivial, but the patient's complaints of persistent ill health and prostration, headache and drowsiness are disproportionate. In such cases alarmingly rapid deterioration may occur, with circulatory collapse or the development of deep coma, or both. Heavy parasitaemia is a constant feature of severe complicated malaria, and the presence of late trophozoites and early schizonts in the peripheral blood should always be regarded as a warning of an impending serious complication such as cerebral malaria.

The indeterminate nature of the fever, the non-specific symptomatology and the frequent absence of splenomegaly are responsible for the high frequency of misdiagnoses, especially of influenza. Infective hepatitis and leptospirosis are also common diagnoses when jaundice is present, and the severity of the headache often leads to a presumptive diagnosis of encephalitis or meningitis. This is avoidable if specific inquiry is made in all febrile patients, especially as to their recent movements, but also as to past visits to malarious or potentially malarious areas.

It is the purpose of this paper to summarise our experience in respect of imported malaria and its serious life-threatening complications which have recently been reviewed *in extenso*,[1] and to stress the fact that each patient is a law unto himself and that most will have more than one of the major complications, notably cerebral malaria, acute renal failure due to acute tubular necrosis, dehydration with extrarenal uraemia, jaundice due to haemolytic anaemia or hepatic failure, and finally acute hypotension with circulatory collapse. Certain other less well-known complications which are brought to light by laboratory investigation will be considered.

During the period January 1965 to December 1972, 50 patients with malaria were admitted to Groote Schuur Hospital, 39 had *P. falciparum* malaria, 10 had serious life-threatening complications and 5 of them died. The clinical course and treatment of these patients were shown graphically, but these will be presented elsewhere, and in this report only a summary of the numerous complications will be presented. Table I summarises the most important features of these patients. The high incidence of renal failure and cerebral malaria and the consistent presence of severe parasitaemia are the most striking features of these cases. Blackwater fever was not present in any of these patients, but patient 10 developed intravenous haemolysis which was attributed to glucose-6-phosphate dehydrogenase deficiency. Table II presents haematological and biochemical data. All patients had markedly raised blood ureas, which were attributable to acute tubular necrosis, except in patients 6 and 7, who had extrarenal uraemia. Hyponatraemia was a consistent finding.

## CEREBRAL MALARIA

All patients except cases 8, 9 and 10 were admitted in deep coma, cases 8 and 9 were semicomatose, while case 5 was admitted moribund, in coma with an unrecordable blood pressure due to acute circulatory failure, and died 3 hours later of cardiac arrest. Case 9 also had an unrecordable blood pressure on admission, but nevertheless made a good recovery. Varying degrees of neck stiffness were observed, but no focal central nervous system signs were detectable. Generalised irregular muscular twitchings were noted in 2 patients and twitching of the mouth and lips in another. Lumbar puncture showed no abnormalities except in patient 10 where cerebrospinal fluid protein was elevated to 100 mg/100 ml, and the presence of parasitised erythrocytes was noted.

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TABLE I. SERIOUS LIFE-THREATENING FALCIPARUM MALARIA

| Patient | Onset to admission (days) | Clinical presentation | Duration of coma before admission (hours) | Admission to diagnosis (hours) | Major clinical involvement | Outcome | Parasite density (percentage of red blood cells) | Immediate cause of death |
|---|---|---|---|---|---|---|---|---|
| 1 | 7 | Coma and jaundice | 48 | 0 | CM, RF | D *19* | 25 | Terminal melaena |
| 2 | 7 | Coma and generalised haemorrhage | 72 | 0 | Haemorrhage, CM, RF | D *36* | 25 | Persistent haemorrhage |
| 3 | 8 | Coma and renal failure | 24 | 8 | CM, RF | D *288* | 90 | Bronchopneumonia |
| 4 | 5 | Anuria, renal failure and semicoma | 24 | 2 | CM, RF | D *312* | 30 | Melaena, pulmonary embolism |
| 5 | 3 | Acute hypotension, collapse and coma | 12 | 0 | CM and circulatory failure | D *3* | 20 | Acute circulatory failure and cardiac arrest |
| 6 | 21 | Coma, hepatic failure, jaundice | 24 | 0 | CM, RF, hepatic failure | R | 90 | — |
| 7 | 14 | Coma and jaundice | 72 | 6 | CM, RF, | R | 95 | — |
| 8 | 10 | Acute hypotension | 12 | 0 | CM, circulatory failure | R | 50 | — |
| 9 | 4 | Semicoma and jaundice | 2 | 0 | CM, RF | R | 60 | — |
| 10 | 4 | Oliguria and renal failure | — | 12 | RF, jaundice | R | 'heavy' | — |

Italicised figures represent hours after admission. CM = cerebral malaria; RF = renal failure; D = death; R = recovery.

TABLE II. COMMON BLOOD AND SERUM ABNORMALITIES IN COMPLICATED FALCIPARUM MALARIA

| Patient | Haemoglobin g/100 ml | Bilirubin mg/100 ml | Platelets $\times 10^3/mm^3$ | Blood-urea mg/100 ml | Sodium mEq/L | Glucose mg/100 ml |
|---|---|---|---|---|---|---|
| 1 | 15 | 13,5/11,6 | 19 | 129 (182)* | 131 | 35 |
| 2 | 11 | 7,4/ 6,6 | 16 | 118 (300) | 109 | 40 |
| 3 | 16 | 2,3/ 1,2 | 256 | 168 (460) | 126 | 80 |
| 4 | 8 | 18,6/ 4,1 | 41 | 68 (360) | 128 | — |
| 5 | 11 | 6,9/ 3,2 | 20 | 81 ( 84) | 128 | — |
| 6 | 11 | 3,6/ 1,2 | 11 | 142 (124) | 113 | 60 |
| 7 | 16 | 6,3/ 3,9 | 60 | 153 (153) | 118 | 90 |
| 8 | 8 | 3,6/ 1,4 | 40 | 177 (217) | 127 | 91 |
| 9 | 9 | 7,3/ 3,9 | 40 | 147 (147) | 130 | 102 |
| 10 | 15 | 6,0/ 3,2 | 356 | 113 (430) | 135 | 120 |

* Bracketed figures represent the peak blood-urea values.

## Acute Renal Failure

It is apparent from Tables I and II that most patients had more than one major complication and that cerebral malaria is very often accompanied by severe acute oliguric renal failure which was present in patients 1 - 7 and 9, and was due to acute tubular necrosis in all except patients 6 and 7, in whom severe extrarenal failure was diagnosed. Acute tubular necrosis was unassociated with cerebral involvement in patient 10, while in patient 4 cerebral symptoms developed 4 days after the onset of anuria.

While the severity and duration of coma undoubtedly contributed to a poor prognosis, other complications such as circulatory collapse, uraemia and haemorrhage determined the final outcome. Thus haemorrhage complicated the course of patients 2 and 4, both of whom were severely uraemic, and in both patients heparin therapy led to a severe aggravation of their bleeding disorders. Terminal gastro-intestinal haemorrhage occurred in patients 1 and 3, both severely uraemic patients who had not received heparin therapy but had received high-dose steroid therapy. All patients had hypotension on admission or at a later stage of their illness. In patients 5 and 10 the blood pressure was unrecordable on admission. Patient 5 was moribund and died of hypotensive circulatory failure with cardiac arrest 3 hours later. Table II records other important features, notably the marked elevation in blood-urea. All patients showed biochemical evidence of jaundice, although in 2 this was not detected clinically. In 2 patients the pattern of bilirubin retention suggested a cholestatic mechanism, while patient 6 had acute hepatic

failure with fetor hepaticus, an elevated cerebrospinal fluid glutamine concentration, and abnormal liver function, as reflected by a raised serum aspartic acid transaminase level.

Thrombocytopenia was present in all but 2 patients and evidence of a disturbance in coagulation, attributable to disseminated intravascular coagulation (DIC), was present only in patients 5, 6, and 7. In patient 6, however, hypofibrinogenaemia and the severe hypoprothrombinaemia were probably due to acute hepatic failure and not a reflection of DIC. Complicating Gram-negative infections affecting the urinary tract and the respiratory system occurred in 2 patients and undoubtedly contributed to the death of patient 3, who developed a fulminant tracheobronchopneumonia after tracheostomy and the use of a positive pressure respirator for acute pulmonary oedema.

Electrolyte disorder, notably hyponatraemia (serum Na <133 mEq/litre), was present in every patient and was due to sodium depletion from vomiting and diarrhoea. This, coupled with over-enthusiastic and ill-considered intravenous therapy, often resulted in overhydration and may have contributed to the fits observed in patient 3. Other complications included hypoglycaemia in 2 patients and metabolic acidosis in 4 patients. Hyperuricaemia was frequently observed on admission, with a peak value of 18,7 mg/100 ml in patient 7. Hypocholesterolaemia 90 - 120 mg/100 ml was also a frequent and persistent finding.

Other interesting observations were the presence of hypocalcaemia in 7 of these patients (6,6 - 8,8 mg/100 ml) which was associated with marked hypo-albuminaemia. Serum creatine phosphokinase, serum lactic dehydrogenase and serum aspartic acid transaminase were elevated significantly in the 6 patients in whom these were studied.

## Treatment

The complexity of the clinical involvement of these cases clearly indicates the necessity for skilled and intelligent assessment of every case diagnosed as one of cerebral malaria. Ideally such cases would be best managed in institutions where intensive nursing care and the necessary biochemical, microbiological and haematological laboratory facilities are available on a 24-hour basis. This is, of course, by no means always feasible, and in any event is not essential if the diagnosis of falciparum malaria is promptly made and appropriate antimalarial therapy commenced without delay. Good nursing care is, of course, desirable. If parasitaemia is severe (>20% of red blood cells) or the clinical picture suggests impending complications, such as persistent severe headaches, with vomiting or diarrhoea, or both, intravenous quinine therapy (650 mg quinine hydrochloride in 200 ml of normal saline) must be commenced immediately and repeated 2 or 3 times at intervals of 8 hours. Intravenous chloroquine can also be used with caution, but the sooner oral or intragastric therapy with chloroquine is started the better. Chloroquine phosphate is often given intramuscularly initially, but in the presence of severe thrombocytopenia (platelets<20,000/mm$^3$) or uraemia, or both, the intravenous route is preferable to avoid haematoma formation.

It would be tedious to detail every aspect of the treatment of patients presented here, but obviously in the presence of renal failure an initial normal dose of the chosen antimalarial drug should be given and subsequently half the usual doses, except during peritoneal dialysis. The treatment for severe cases includes normal scrupulous attention to fluid and electrolyte balance, and where renal failure is present the institution of the Giovanetti diet is obviously indicated, bearing in mind, however, that these patients are often hypo-albuminaemic and intravenous human albumin or plasma may be required. Owing to a propensity to develop pulmonary oedema, overhydration must be avoided. Acidosis should be corrected with intravenous sodium bicarbonate. In severely oliguric or overhydrated patients, furosemide is worth a trial in doses increasing up to 500 mg/day. The institution of peritoneal dialysis should not be delayed in the presence of severe anuric or oliguric renal failure with a rapidly rising blood-urea. In the event of severe circulatory collapse, continuous intravenous isoprenaline sulphate infusion is indicated, and in the event of acute hepatic failure vitamin K should be given. Blood transfusion will be necessary in the presence of severe anaemia or bleeding. High steroid dosage (hydrocortisone, dexamethasone, or 6-methyl prednisolone) is recommended for a period of 48 hours at least, or until the critical phase is past. A single slow infusion of rheomacrodex (500 ml) may help to prevent sludging in the cerebral microcirculation.

A vexing and generally very difficult decision concerns the institution of anticoagulant therapy with heparin. It is my belief that the frequency of DIC in cerebral malaria is overemphasised, and that heparin therapy as in cases 2 and 4 is dangerous, since the severe uraemic state itself is characterised by a severe defect in blood coagulation. Heparin should, therefore, be withheld in such cases. I remain unconvinced of the merits of its routine use, as recommended by Mitchell.[2] I reiterate that thrombocytopenia is a constant feature of the acute malaria, irrespective of the type of malaria or the severity of the attack, and that its presence should only alert the doctor to the possibility of DIC. Thrombocytopenia is largely attributable to splenic sequestration[3] and heparin therapy is indicated only when there is clinical evidence of a generalised bleeding state and when the coagulation profile shows unequivocal evidence of DIC (Table III). The opinion of some authorities is that for a diagnosis of DIC

**TABLE III. THE COAGULATION PROFILES OF DISSEMINATED INTRAVASCULAR COAGULATION AND PATHOLOGICAL FIBRINOLYSIS**

| | Intravascular coagulation | Pathological fibrinolysis |
|---|---|---|
| **Platelets** | **Decreased** | **Normal** |
| **Fibrinogen** | **Reduced** | **May be reduced** |
| **Euglobulin lysis time** | **Normal** | **Reduced** |
| **Prothrombin index** | **Decreased** | **Decreased** |
| **Kaolin clotting time** | **Prolonged** | **Prolonged** |
| **Fibrin inhibition test** | **Usually positive** | **Usually negative** |

the following abnormalities should be present: thrombocytopenia, hypofibrinogenaemia and hypoprothrombinaemia, but ideally all 6 parameters listed under intravascular coagulation should be present.

Finally I need to emphasise that severely-ill patients may have other complicating illnesses, particularly salmonella infections. In Gelfand's recent report falciparum malaria appears to have been an incidental finding.[4] One of his cases of haemoglobinuria is associated with typhoid fever. Coincidental glucose-6-phosphate dehydrogenase deficiency with haemoglobinuria must always be kept in mind, since blackwater fever is a rare complication of malaria.

REFERENCES

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4. Gelfand, M. (1972): Trop. Geogr. Med., **24**, 18.