Lesson of the Week

Fatal falciparum malaria and the availability of parenteral antimalarial drugs in hospitals

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The incidence of cases of malaria imported into the United Kingdom has increased.[1] [2] Early and appropriate treatment in severe cases is vital, but hospital pharmacies may not always stock parenteral antimalarial drugs. We report on a case of fatal falciparum malaria in a patient on long-term steroid treatment and suggest that parenteral antimalarial drugs should always be available in district general hospitals in England and Wales that admit patients with acute illness.

> **Steroid-dependent patients are vulnerable to overwhelming infection with falciparum malaria and other parasites. Parenteral antimalarial drugs should be available in all hospitals admitting acutely ill patients**
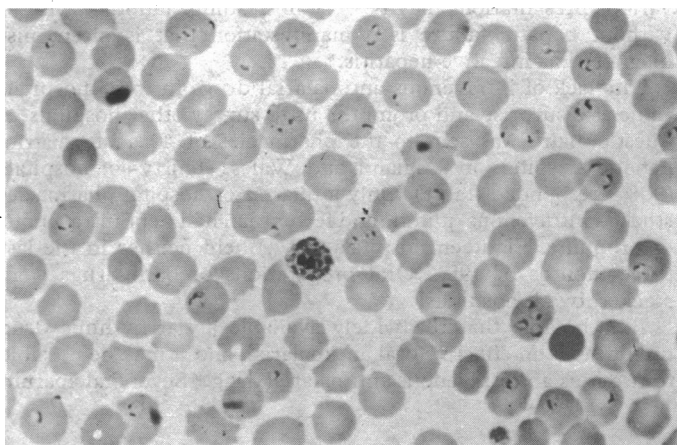
Case report

A 63-year-old Caucasian engineer was admitted to hospital one week after returning to England from Nigeria. His illness began in Nigeria with a two-day episode of diarrhoea, vomiting, and fever. On returning to this country his symptoms recurred and he also became jaundiced, with dark urine and pale loose stools. His symptoms improved after three days and he was diagnosed as having infectious hepatitis. Two days later, however, he was admitted to hospital because the symptoms had returned and his clinical condition was deteriorating rapidly. He had been an asthmatic for 10 years and took prednisolone 10 mg daily and salbutamol by inhaler. Although he frequently travelled to endemic malarious areas he did not take regular antimalarial prophylaxis.

On physical examination he was drowsy and confused, febrile (38·5°C), jaundiced, and dehydrated with cold extremities. His pulse rate was 150/minute and regular, and his blood pressure was 140/90 mm Hg. He was tachypnoeic, with generalised bronchospasm. The liver was tender and enlarged 5 cm below the costal margin, and the tip of the spleen was palpable. There were no focal neurological signs.

The haemoglobin concentration was 13·0 g/dl, white cell count 14·8 × 10⁹/l (14 000/mm³), with a differential cell count of 72% neutrophils, 26% lymphocytes, 2% monocytes, and platelets 80 × 10⁹/l (80 000/mm³). The results of urine analysis showed haemoglobinuria and bilirubinuria. A thin blood film showed heavy infestation with ringed trophozoite forms of *Plasmodium falciparum* (figure). The parasite concentration was 3·5 × 10⁹/l, and 55% of the erythrocytes contained parasites. The results of biochemical investigations showed urea 33·1 mmol/l (187 mg/100 ml) (normal 2·5-7·5 mmol/l; 15-45 mg/100 ml); creatinine 229 μmol/l (2·6 mg/100 ml) (normal 50-115 μmol/l; 0·56-1·3 mg/100 ml); bilirubin 76 μmol/l (4·4 mg/100 ml) (normal 5-17 μmol/l;

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Photomicrograph of peripheral blood film showing trophozoites and a schizont of *Plasmodium falciparum*. Leishman stain × 1000 (original magnification).

0·3-0·99 mg/100 ml); lactate dehydrogenase 600 U/l (normal 90-300 U/l); aspartate aminotransferase 179 U/l (normal 10-50 U/l); alkaline phosphatase 80 U/l (normal 35-85 U/l). Arterial blood gas analysis showed a metabolic acidosis with respiratory compensation: pH 7·27, standard bicarbonate 10·1 mmol(mEq)/l, Po₂ 10·6 kPa (80 mm Hg), Pco₂ 2·9 kPa (22 mm Hg). An electrocardiographic examination showed sinus tachycardia, and a chest radiograph was normal.

Because the infection was so severe we decided to start treatment with intravenous chloroquine, but no parenteral chloroquine or quinine was available in this or two neighbouring hospitals. Supportive treatment was given to the patient while the drug was obtained urgently from a fourth hospital. He had a cardiac arrest, however, before the drug was received. Resuscitation was unsuccessful, and he died five hours after admission. Necropsy examination confirmed that he had had an overwhelming malarial infection. The liver (weight 1800 g) and spleen (weight 400 g) were enlarged and contained malarial pigment, which was also found in all other organs. The brain (weight 1440 g) and lungs (weight 1180 g) were oedematous and had

widespread perivascular haemorrhages. Many of the glomerular capillaries were plugged with fibrin thrombi, and the kidneys also showed benign nephrosclerosis. The intimal surfaces of the heart and aorta were stained pinkish-brown owing to intravascular haemolysis. The adrenal glands were atrophied, consistent with long-term steroid treatment. The heart (weight 420 g) showed patchy fibrosis, and the anterior descending branch of the left coronary artery showed an old subtotal occlusion by atheroma.

Discussion

In 1976, 534 cases of malaria were reported in Britain, of which 93 were due to *Plasmodium falciparum*.[1] In 1980, 1670 cases were reported, including 405 cases due to *P falciparum*, leading to seven deaths.[2] In one survey in Thailand only 10% of patients with falciparum malaria had a parasite concentration of more than $0.1 \times 10^9/l$ (100 000/mm³).[3] Our patient had a remarkably high parasite concentration of $3.5 \times 10^9/l$ (3 500 000/mm³), which could be explained by immunosuppression owing to long-term steroid treatment and also by the delay in diagnosis. Steroid treatment in mice infected with malaria results in higher parasitaemias and lowered antibody responses.[4] ACTH increases the parasitaemia of induced malaria in man.[5] Patients who are steroid-dependent and their doctors should therefore be particularly aware of the additional hazard of visiting endemic malarious areas. Recent reviews have discussed appropriate antimalarial prophylaxis[6] and common reasons for misdiagnosis.[7] There is little that is typical about falciparum malaria, and its various presentations may be very misleading. Jaundice with or without hepatic failure is a manifestation that is often misdiagnosed as infective hepatitis.[8]

The lack of intravenous antimalarial drugs in three hospitals came as a surprise and prompted us to survey other hospitals. A questionnaire was sent to the pharmacies of 40 acute district general hospitals in England and Wales. Thirty-six hospitals (90%) responded (table). Only a quarter of hospital pharmacies stocked intravenous quinine and fewer than half kept intravenous chloroquine. Eighteen hospitals (50%) held neither in the last three months of 1981. Oral preparations of both drugs were stocked by all hospitals.

It is notable that the widely available antiarrhythmic drug quinidine is an effective oral antimalarial, and it may be possible to use it as an intravenous antimalarial drug.[9] Severe falciparum malaria should, however, be treated with an intravenous infusion of chloroquine or quinine, depending on where the disease was acquired, and with appropriate supportive treatment.[10] Up-to-date information on the distribution of chloroquine-resistant strains of *P falciparum* may be obtained from several institutions.[6]

Availability of parenteral chloroquine and quinine in 36 district general hospitals in 1981

	No (%) of hospitals	
	With drug	Without drug
Intravenous quinine	9 (25)	27 (75)
Intravenous chloroquine	16 (44)	20 (56)

Because of the high mortality in patients with severe falciparum malaria parenteral antimalarial drugs should be readily available in all hospitals that admit acutely ill patients.

We thank the pharmacies of all the hospitals who provided information in the survey.

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A 16-year-old asymptomatic girl developed heavy melaena followed by haematemesis and despite substantial blood transfusion required emergency laparotomy. She died on the operating table from haemorrhage from extensive varices of the stomach and oesophagus. Necropsy showed an abnormally large left lobe of the liver with an abnormal portal vein entering the left lobe, and a portal caval anastomosis of an aberrant portal vein to the inferior vena cava. She had a completely healthy sister of 14. Is investigation of the surviving sister justified, and if so what procedures would be reasonable?

Portal hypertension is rare in teenagers, and since many of the causes are associated with hereditary disorders it is most important to screen siblings for evidence of liver disease, regardless of their apparent wellbeing. It is not uncommon for the first symptom to be catastrophic variceal haemorrhage. The causes of portal hypertension may be cirrhotic or non-cirrhotic. Cirrhosis may be confirmed or excluded by histological examination of a specimen of liver obtained at necropsy. If present Wilson's disease, mucoviscidosis, and α_1-antitrypsin deficiency are the commonest causes in England, but it may be difficult to confirm the first two on histological criteria alone. Congenital hepatic fibrosis is the commonest cause of non-cirrhotic portal hypertension at this age and this too is familial, although a wide range of hepatic and renal abnormalities may also be found.[1] Developmental anomalies in the anatomical structure of the liver are not necessarily of any pathological importance, while pronounced alterations in the portal venous system can arise secondary to the established portal hypertension.

The healthy sister should have a full physical examination with particular regard to cutaneous features of liver disease as well as enlargement of the liver or spleen, and routine liver function tests should be performed. If there is any possibility of Wilson's disease serum caeruloplasmin and urine copper excretion should also be estimated, while a barium swallow should be carried out if congenital hepatic fibrosis is suspected. Liver disease should be documented in such patients even if there is no prospect of immediate treatment, since a background knowledge of the problem will ensure much more effective treatment of future complications, such as variceal haemorrhage, when they arise.—D R TRIGER, consultant physician, Sheffield.

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