Severe Malarial Infection in a Patient with Sickle-cell Anaemia

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During a retrospective survey of the recorded causes of death among Nigerians with homozygous sickle-cell disease (SS) on whom necropsies were performed at University College Hospital, Ibadan, we encountered the unusual case of an 8-year-old Nigerian girl who died from severe infection with *Plasmodium falciparum* and *P. malariae* (Adeloye *et al.*, 1970). Rey *et al.* (1966) reported the death from *P. falciparum* of a 10-year-old boy from Dakar with the signs and symptoms of sickle-cell anaemia, but the haemoglobin genotype of their patient was not established. In view of this the following case probably represents the first authentic account of the occurrence of severe malarial infection contributing to death in a sufferer from homozygous sickle-cell disease.

Case Report

A Nigerian girl aged 7 was referred from another hospital on 14 July 1961 with severe anaemia, fever, and cough. She had been ill for three years with intermittent attacks of "yellow eyes" and "rheumatic" painful swelling of the joints, which were worse during the rainy seasons and after a cold bath. On examination she was severely anaemic and lethargic, with a regular pulse of 116, a blood pressure of 90/40 mm Hg, and a systolic murmur over her precordium. Haemoglobin was 2·1 g/100 ml (14%), and the blood film showed numerous nucleated red and sickle cells. Her haemoglobin electrophoresis showed a single band of haemoglobin S, so that a diagnosis of crisis in sickle-cell anaemia was made. She was treated with folic acid and later discharged home on the same medication and advised to take regular antimalarial drugs. No blood transfusion was given.

She was next seen 7 September 1962 with a two-day history of fever, pallor of skin, and jaundice. She was very anaemic with temperature of 103°F (39·4°C). She had a regular, collapsing pulse of 140, a systolic apical murmur, a blood pressure of 120/50 mm Hg, and raised jugular venous pressure. The liver was enlarged four finger's breadths and tender. There was no ascites. and the spleen was not palpable. Haemoglobin was 3·8 g/100 ml and the peripheral blood film showed numerous rings, band-forms, and gametocytes of *P. malariae* and *P. falciparum*, pronounced polychromasia, many target cells, nucleated red blood cells, and a few sickle-cell forms. The urine contained excess urobilinogen. She was treated with chloroquine sulphate intramuscularly and folic acid but rapidly deteriorated and died within 48 hours of admission.

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NECROPSY FINDINGS

Macroscopic Features.—The frontal bones were thickened and their diploë contained red marrow. Brain was pale and wet, without any haemorrhages. Pericardial sac contained about 5 ml of yellow fluid and the heart weighed 155 g. The liver was grossly enlarged, weighing 1,355 g (normal for her age being 254 g), and firm with a deep purplish coloration. The spleen was atrophic, being represented by a small piece of greyish white tissue which weighed only 3·0 g.

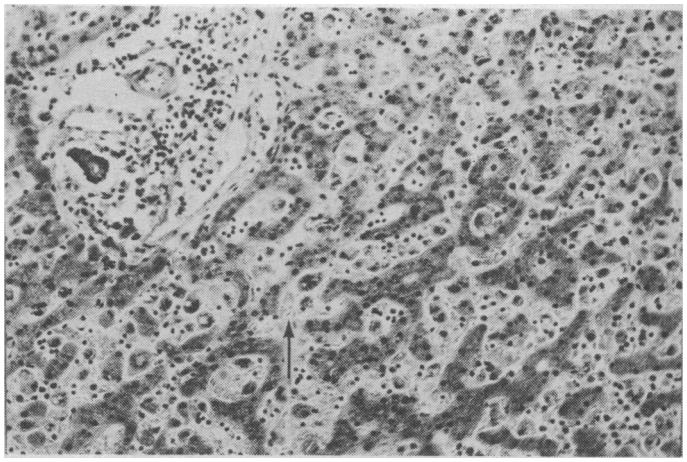

FIG. 1—Histological section of liver showing mild lymphocytic infiltration of the portal tract, pronounced dilatation of the sinusoids, presence of sickled erythrocytes (arrow), and numerous Kuppfer cells with erythrophagocytosis and abundant dark (malarial) pigment granules. The parenchymal cells are compressed by the dilated sinusoids and contain some haemosiderin granules. (H. & E. × 150.)

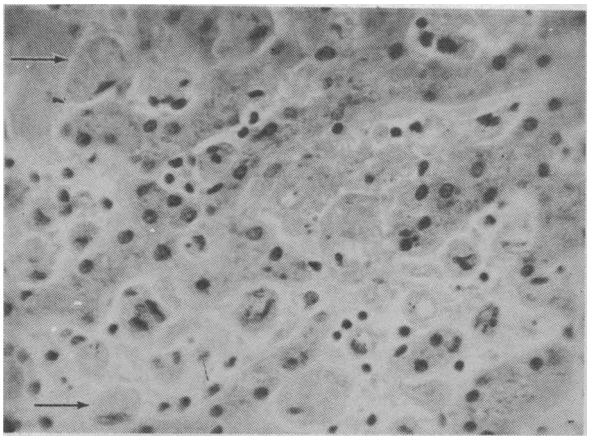

FIG. 2—High-power magnification showing dilated sinusoids containing many sickled erythrocytes, several Kuppfer cells with dark (malarial) pigment granules, and a few showing erythrophagocytosis (arrows). (H. & E.)

Microscopical Features.—Kidney: scanty to moderate amount of pigment in the capillaries of the glomerular tufts. Liver cells contained haemosiderin. The sinusoids were greatly distended, and sickled erythrocytes could be seen in them. The Kuppfer cells were much enlarged and contained red cells and pigment which was partly iron positive but mostly iron negative, the latter presumably being malarial pigment (haemozoin) (Figs. 1 and 2). An area of haemorrhagic infarction in the spleen was surrounded by thick-walled vessels which contained iron pigment in their walls. The rest of the tissue was composed mostly of siderofibrotic tissue.

In summary, the necropsy findings confirmed acute severe malarial infection in a subject with sickle-cell anaemia.

Comment

Death from *P. falciparum* infection in subjects who live in areas of stable malaria is usually due either to cerebral involvement or to the consequences of anaemia (Edington and Gilles, 1969).

Almost all the data on increased resistance against malaria have been obtained in A/S heterozygotes, and there is no a priori reason to expect that they should apply to S/S homozygotes. In addition, one can envisage some mechanisms whereby malaria might actually lead to death in the homozygote. (1) A patient with sickle-cell disease suffers from chronic anaemia. The superimposed haemolysis from acute malaria infection may precipitate anaemic heart failure. This occurred in our case. (2) Malaria might act as a trigger for intravascular sickling (Edington, 1953). Parasitized cells from A/S heterozygotes tend to sickle more readily than non-parasitized cells (Luzzatto *et al.*, 1970), a phenomenon which facilitates their trapping by a normal reticuloendothelial system. However, when a major component of that system, the spleen, is atrophied as a result of sickle-cell disease (as in our patient), parasitized cells will continue to circulate and the parasitaemia may threaten life.

In conclusion, we suggest that in our case, and in that of Rey *et al.* (1966), the S gene in double dose failed to protect against severe malaria and the peculiar interaction between this genetic abnormality and malarial infection led to the fatal outcome.

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Manifestation of Hereditary Fructose Intolerance

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Haemostatic failure in early infancy, when associated with prolongation of the prothrombin time, is usually ascribed to "haemorrhagic disease of the newborn." This disease is a temporary deficiency of the vitamin-K dependent coagulation factors II, VII, IX, and X, and it responds to the administration of vitamin K. The following case reports illustrate a more unusual cause of prolongation of the prothrombin time in two siblings with haemostatic failure.

Case 1

A male infant, the third child of healthy unrelated parents whose previous two children were well, was born at term after an uneventful pregnancy; birth weight 3,800 g. He was discharged home at 48 hours on a cow's milk formula and did not receive additional vitamin K. At 9 days he was readmitted in extremis and died soon afterwards of massive subarachnoid and gastrointestinal bleeding. The prothrombin time on admission was longer than 60 seconds. Necropsy confirmed the diagnosis of subarachnoid haemorrage and a firm yellow brown liver was found, histological examination of which showed widespread parenchymal cell necrosis with massive fatty infiltration and early bile duct proliferation (see Fig.). Because the prothrombin time had been greatly prolonged a diagnosis of haemorrhagic disease of the newborn had been made; the hepatocellular necrosis was unexplained at the time.

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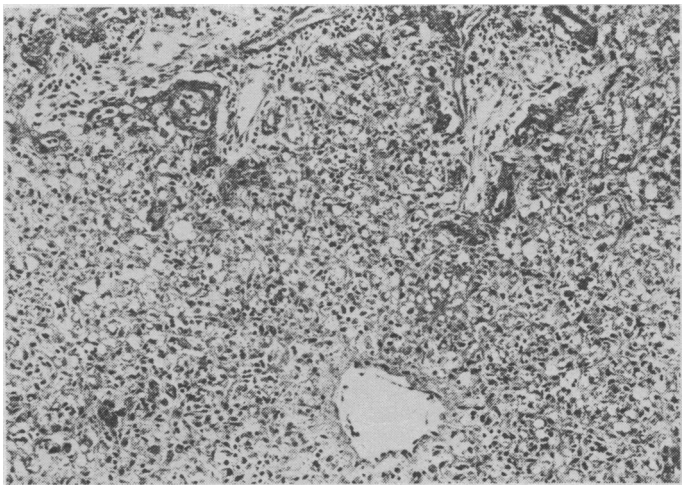

Case 1. Liver specimen showing extensive parenchymal cell necrosis, with fatty vacuolation and non-specific cellular infiltration. Proliferation of bile ducts is seen in the upper part of the field. (Haematoxylin and eosin. x84.)

Case 2

This infant, the sister of Case 1, was born also at term after a normal pregnancy; birth weight 3,080 g. She received vitamin K_1 (Konakion) 1 mg intramuscularly after birth and was fed with a cow's milk formula. At 3 weeks she was readmitted because she was vomiting and weighed 300 g less than at birth. Her umbilicus was infected but she did not have hepatosplenomegaly and there were no other abnormal physical signs. Femoral venepuncture resulted in a large haematoma and continuous oozing of blood for over 10 hours.

Coagulation studies (see Table) showed not only abnormalities of the vitamin-K dependent factors VII and X but also a reduction in factor V and fibrinogen and an increase in factor VIII. There was no response to parenteral administration of vitamin K. These features were strongly suggestive of severe liver disease. At this stage she became clinically jaundiced (bilirubin: total 5 mg/100 ml, conjugated 3 mg/100 ml) and other tests of hepatocellular function became abnormal (5-nucleotidase 191 IU, lactic dehydrogenase 630 IU, isocitrate dehydrogenase 120 IU).

The early onset of a familial haemorrhagic tendency and hepatic damage was suggestive of an inborn error of metabolism. Normal red-cell levels of galactose-1-phosphate uridyl transferase excluded diagnosis of galoctosaemia. The presence of fructose in the urine, together with estimations of blood sugars which showed higher levels of total reducing substances than of glucose (glucose oxidase