Disseminated Intravascular Coagulation with Fatal Haemorrhage in Cerebral Malaria

British Medical Journal, 1970, 2, 710

Disseminated intravascular coagulation has been incriminated as an intermediary mechanism in the pathogenesis of a wide spectrum of diseases (Mackay, 1965), including cerebral malaria (Devakul, Harinasuta, and Reid, 1966). In view of the current interest in the subject we report a fatal case of cerebral malaria in which disseminated intravascular coagulation was sufficiently pronounced to produce clinical bleeding.

CASE REPORT

A 22-year-old white man felt "off colour" 10 days after returning from a camping trip in Mozambique, 100 miles (160 km) north of Lourenço Marques. This is an endemic malarial area, but he had not taken prophylactic antimalarials. Six days later he was noticed to have become rather slow mentally, and on that day started to bleed from the nose, urethra, and rectum. Physical examination at this time showed him to be confused, disorientated, stuporous, and bleeding from the nose. His temperature was 100°F. (37.8°C.), pulse 110, and blood pressure 90/60. The skin and mucous membranes were pale. Purpura was not present. Blood was noted at the external urethral meatus, but rectal examination failed to show any blood or melaena stool. The spleen was palpated 2 cm. below the costal margin. There were no localizing neurological signs, and the remainder of the physical examination disclosed nothing of significance. A blood count showed a haemoglobin concentration of 12.3 g./100 ml., reticulocytes 3%, leucocytes 14,200/cu.mm., and platelets 46,000/cu.mm. The blood smear showed some schistocytosis of the red cells and a heavy infestation with *Plasmodium falciparum*. The diagnosis of cerebral malaria was made and intravascular coagulation was suspected in view of the bleeding and thrombocytopenia. Coagulation studies showed low levels of fibrinogen, factor V, and factor VIII, without evidence of increased fibrinolysis (see Table). The plasma haemoglobin concentration was 55.1 mg./100 ml. chloroquine, quinine, and heparin were administered intravenously, followed by 3 g. of fibrinogen 30 minutes later and 1 unit of fresh blood. The dose of heparin was 7,500 units every six hours. On starting this therapy the bleeding stopped, but his mental state deteriorated steadily until he was deeply comatose. Twelve hours after admission to hospital there was a large haematemesis and melaena, followed by a sudden fall in blood pressure and death. Permission for necropsy was refused.

Results of Coagulation Tests

Single-stage prothrombin time	14.5 sec. (control 9.9 sec.)
Thrombin time	24.0 sec. (control 14.0 sec.)
Kaolin partial thromboplastin time	90.3 sec. (control 39.8 sec.)
Fibrinogen	79 mg./100 ml. (normal 200-400 mg./100 ml.)
Factor VIII	20% (normal 50-150%)
Factor V	52% (normal 50-150%)
Euglobulin lysis time	24 hours (normal 6 hours)
Fibrin plates for fibrinolysis	Negative
Fibrinogen degeneration products	Negative
Plasminogen	4.6 casein units (normal 1-5)

COMMENT

Haemorrhage in association with thrombocytopenia, fibrinogenopenia, and low levels of factors V and VIII leaves little doubt about the presence of disseminated intravascular

coagulation in this patient. There was no evidence of secondary increased fibrinolysis, for the euglobulin lysis time was prolonged, fibrinolysis could not be shown on a fibrin plate, fibrinogen degeneration products were not detected immunologically, and the plasminogen level was normal. Failure to show increased fibrinolysis is similar to the findings of Dennis, Eichelberger, Inman, and Conrad (1967), who reported prolonged euglobulin lysis times in falciparum malaria. It would appear that the fibrinogenopenia which may occur in malaria is the result of disseminated intravascular coagulation without detectable secondary stimulation of the fibrinolytic system.

Dennis *et al.* (1967) studied 31 American soldiers evacuated from Vietnam with chloroquine-resistant falciparum malaria. During relapse there was prolongation of the prothrombin time, thrombin time, and partial thromboplastin time, with reduction of factors I, V, VII, VIII, X, and thrombocytopenia. The euglobulin lysis times were prolonged. The more severely ill the patient the greater the degree of coagulation abnormality. During convalescence most of these tests returned to normal.

The mechanism whereby malaria induces disseminated intravascular coagulation is not known, but is possibly via intravascular haemolysis with release of coagulant materials, such as phosphatidylserine and phosphatidylethanolamine from the lysed red cells. These phospholipids are active procoagulants and may initiate intravascular coagulation (Bradlow, 1961). *P. falciparum* malaria can result in pronounced intravascular haemolysis as in the present case, in which the plasma haemoglobin concentration rose to 55 mg./100 ml.

There is evidence that the presence of disseminated intravascular coagulation may add to the morbidity and mortality of falciparum malaria. In three patients treated with heparin to control disseminated intravascular coagulation there was rapid improvement in the clinical state and laboratory tests (Dennis *et al.*, 1967). This improvement, however, may not have been due entirely to the anticoagulant effect of heparin, for the drug has antimalarial activity as well (Dennis and Conrad, 1968). It is probable that in the present case heparin was started too late to affect the course of the disease. Heparin should be administered to all patients with cerebral malaria who show thrombocytopenia and/or fibrinogenopenia. Anti-fibrinolytic agents are contraindicated.

We wish to thank the Director, South African Institute for Medical Research, for laboratory facilities, and Dr. K. Stevens for referring the patient for coagulation studies.

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