Clinical Problems

New Concepts in Treatment of Malignant Tertian Malaria with Cerebral Involvement

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Summary

Of 140 patients with malignant tertian malaria seen during 1956 to 1967 10 died. Death was caused by cerebral malaria in all cases. Since 1968 more intensified treatment has resulted in the complete recovery of three patients and the partial recovery of one, all of whom had been in a cerebral malaria coma for various periods of time before admission and in whom a fatal outcome was expected. In these cases a polypragmatic therapeutic approach using intravenous low molecular weight dextran, besides the usual quinine and fluids, corticosteroids, heparin and urea, separately or combined, was adopted.

Introduction

Malaria due to infection with *Plasmodium falciparum* is easily cured so long as the diagnosis is made in the early stages. In the untreated case parasitaemia increases as the disease progresses. Though pernicious attacks may develop at any stage of the disease they usually occur in untreated patients with a high parasitaemia. The pernicious forms of malignant tertian malaria cause various clinical syndromes, depending on the changes produced in various organs. Cerebral malaria is one of the most serious complications, being progressive and leading to death unless treatment is begun early. Impairment of kidney function can dominate the clinical picture, and pulmonary oedema may be fatal during any stage of the disease.

From 1956 to 1967 10 patients died from cerebral malaria; all were admitted to our hospital in deep coma, and immediate intravenous administration of quinine was unsuccessful, even though exact fluid and electrolyte balance was maintained. Since that time we have added intravenous hydrocortisone[1] to our treatment regimen, and on occasions we have also used heparin, low molecular weight dextran, and urea. We believe that these new measures have been life-saving in several cases.

Present Study

Immediately after admission a routine thick smear was taken from all patients arriving from overseas who had recently been in potentially dangerous areas, even when their complaints and symptoms were not indicative of malaria. As a result several *P. falciparum* infections were found in patients who did not show the typical signs and symptoms.

TREATMENT

Oral chloroquine was given to most of the patients who were not seriously ill on admission, and all recovered. Intravenous quinine was given to 41 patients by slow intravenous infusion in 5% glucose solution in maximum doses of 2 g every 24 hours.

Intravenous quinine was used when one or more of the following indications were present: (1) a high parasitaemia in the peripheral blood, with the presence of schizonts besides the usual trophozoites; (2) a high temperature combined with shock, diarrhoea, and vomiting; and (3) signs and symptoms indicating involvement of the brain, liver, or kidneys.

Low molecular weight dextran was given rapidly by separate intravenous infusions of 500 ml every 24 hours only when cerebral coma or severe impairment of kidney function was present. In similar cases glucocorticosteroids were given either as dexamethasone, 24 mg every 24 hours, or as prednisolone, 100 mg every 24 hours. Urea was used only once in a single dose of 45 g intravenously. Heparin was given in 50-mg doses every six hours over at least 48 hours.

CASE 1

A 26-year-old Norwegian sailor coming from the West African coast had developed a fever eight days before admission and had lapsed into a coma within the last 24 hours. He was very dehydrated and showed no response to verbal or painful stimuli. There was no neck stiffness and tendon reflexes were still positive. The thick smear showed heavy parasitaemia with *P. falciparum* trophozoites and schizonts. Therapy was started immediately with an intravenous 5% glucose infusion containing quinine-urethane, heparin, and dexamethasone. Amazingly, he regained consciousness one hour later. Intravenous therapy was stopped after 48 hours and recovery was complete.

Comment.—From our previous experience, cerebral malaria coma lasting 24 hours was practically always fatal. The combination of quinine with heparin and especially with dexamethasone resulted in an unexpectedly quick recovery.

CASE 2

A 25-year-old British sailor was admitted to hospital on 15 May 1969, having left Dakar on 1 May. He had had a fever for three hours before admission. He was deeply comatose, and his temper-

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ature was 38·9°C, pulse rate 112 beats/minute, and blood pressure 110/70 mm Hg. The spleen was palpable 2 cm below the left costal margin. Apart from the coma no neurological abnormalities were noted. Laboratory investigations showed a large number of falciparum malaria trophozoites and schizonts in the blood. Intravenous therapy with low molecular weight dextran, quinine prednisolone, and heparin was started immediately.

Next day there was no improvement. His temperature rose to 40·2°C. Again, no neck stiffness was noted, but a positive Babinski reflex was seen bilaterally. Lumbar puncture showed a raised pressure of 30 cm and xanthochromia, probably due to haemolysis. Intravenous therapy was continued as before and fluid balance was maintained, though there was a moderate rise in the blood urea and creatinine levels.

On the morning of 19 May he regained consciousness, more than 84 hours after admission, and was soon able to eat and drink. His temperature was normal and the parasitaemia had disappeared. Antimalarial treatment with quinine by mouth was continued. Recovery was gradual; no neurological after-effects were seen. The electroencephalogram on 29 May was entirely normal.

Comment.—This was the first patient we had ever seen who recovered having been in malaria coma for over three days. The combination of quinine, heparin, prednisolone, and low molecular weight dextran undoubtedly played an important part. It is impossible to evaluate which preparation, besides quinine, was the most beneficial.

CASE 3

A 48-year-old seaman from India was admitted to hospital on 25 August 1969. His ship came from the West African coast and his main complaint was persistent hiccup with diffuse pain in the upper abdomen and lower chest. His temperature was 39·1°C and rose later during the day to 41·1°C. Blood pressure was 160/100 mm Hg, and pulse rate 100/minute. No abnormalities were found, but the thick smear showed a high parasitaemia of *P. falciparum*.

The patient was well orientated and mentally completely clear and alert. He did not show any abnormal neurological signs and symptoms. Because of the high parasitaemia he was given an intravenous 5% glucose infusion containing 500 mg of quinine-urethane. A few hours later he became confused and excited and verbal contact was lost; subsequently he became unconscious. Treatment was intensified by giving low molecular weight dextran, prednisolone, heparin, and another 500 mg of quinine-urethane during the next 24 hours.

On 26 August consciousness gradually returned, diuresis was pronounced, and fluid balance was maintained. Next day his temperature was down to 37·5°C; he was conscious, could eat and drink normally, and intravenous fluids and drugs were discontinued. Chloroquine 200 mg was given by mouth.

On the morning of 29 August the patient's temperature was 36·0°C, but to our surprise he could not be awakened. He was completely comatose and did not react to any stimuli. There was moderate stiffness of the neck, pupil and corneal reflexes were present, and the tendon reflexes were diminished in the left leg.

Intravenous fluids containing quinine, low molecular weight dextran, prednisolone, and heparin were resumed. To combat the cerebral oedema 45 g of urea was given intravenously over 15 minutes. A diuresis of 5,000 ml compared with a fluid intake of 3,250 ml ensued.

Though that evening he seemed moribund, the next day he was still alive and responded to stimuli. He remained drowsy, but during the following day gradually returned again to normal. Treatment was completed with chloroquine by mouth and he was discharged in good health 10 days later.

Comment.—It seemed to us that the recovery from the second period of coma was mainly due to the urea dehydration.

CASE 4

A 30-year-old Chinese sailor was admitted to hospital on 6 February 1970. He came by ship from West Africa and had had a fever for one week. No specific treatment was given and no malaria prophylactic agent was taken. On admission he had a high fever, neck stiffness, and was semicomatose. Forty per cent. of the erythrocytes contained parasites, and kidney function had deteriorated, with albuminuria and raised creatinine (2·2-3 mg/100 ml) and blood urea (94 mg/100 ml) levels.

With the combined treatment of quinine, low molecular weight dextran, heparin, and prednisolone his temperature came down to normal and the cerebral symptoms disappeared completely. A thick blood smear did not show any parasitaemia after two days.

The patient's kidney function did not improve, however, and he started to complain of severe abdominal pain in the left kidney region. Heparin was discontinued. Though the daily intake of water and sodium was carefully kept below the daily output, eight days after admission and without any signs of overhydration he suddenly developed a fulminant pulmonary oedema and died within a few hours.

At necropsy no intravascular clotting could be shown in any capillary system. The presence of a perirenal haematoma explained the pain in the left kidney region. There was massive pulmonary oedema, with occasional hyaline membranes. No haemorrhage was seen in the brain. No specific signs of acute malaria encephalopathy were seen either macroscopically or microscopically. In general the microscopical pattern of cerebral changes corresonded rather to non-specific subacute encephalopathy with oedema and inflammatory reactions. Parasites were still present in the capillaries of several organs.

Comment.—It was not possible to effect dehydration with urea in this patient because of his impaired kidney function. Despite continuous quinine therapy parasites were still present in the organs long after they had disappeared from the peripheral blood.

Discussion

The death of 10 patients in our hospital during 1956 to 1967 is not unusual when compared with figures from comparable centres elsewhere in Europe. Shute and Maryon[2] reported 58 deaths apparently due to malaria in the United Kingdom between 1954 and 1969. Mohr[3] saw eight fatal cases in sailors in Hamburg between 1961 and 1968. Nine malaria fatalities were reported in the U.S.A. in 1969;[4] only four of these patients had done military service in Vietnam; while of the five civilian deaths four occurred in persons who had recently returned from Africa.

PATHOGENESIS

The pathogenesis of malignant tertian malaria has been extensively described by Maigraith,[5] who considers anoxia to be of primary importance. Primarily this anoxia affects the endothelial lining of the capillaries because of margination—in other words, adhesion of parasitized erythrocytes to the capillary vessel wall. It also leads to permeability of the capillary wall, leakage of abnormal amounts of fluid into the surrounding tissues, and diapedesis of cells. This loss of fluid can lead to intravascular concentration of cells, agglutination, sludging, further stasis, and progressive anoxia. The sludging and thrombosis, seen at necropsy, especially in the cerebral capillaries, are secondary to the initial disintegration of the endothelial lining of the capillaries. This picture is similar to that seen in inflammation produced by bacterial infection or immunological reactions. Whether a cytotoxic mechanism also has a role in pathogenesis is still undecided.

Recently, Devakul *et al.*[6] suggested that intravascular coagulation may be important in producing intravascular changes in *P. falciparum* infections. They showed a precipitous fall in plasma fibrinogen in two patients who had a severe illness highly resistant to chloroquine. Nevertheless, this concept must presuppose that such capillary stasis is reversible. If blocking of vessels was due exclusively to thrombosis of parasitized cells, with adherence to the vessel wall, this process would

not be rapidly reversible and clinical recovery would be improbable.

The possibility of clinical recovery must be borne in mind on every occasion that one or more organs are involved in a *P. falciparum* infection. The most serious and life-threatening complication is severe cerebral infection, but renal, pulmonary, and hepatic disturbances can be equally dangerous.

AIMS OF THERAPY

(1) The first aim of therapy should be the destruction of the malaria parasites. Administration of 1-2 g of quinine intravenously every 24 hours results in optimal blood levels in the shortest possible time. Though many antimalarial drugs are normally rapidly absorbed from the gastrointestinal tract, administration by mouth is often impossible or, even if possible in semicomatose states, hazardous. Absorption in critically ill patients is inevitably uncertain—for example, gastrointestinal motility and splanchnic circulation may both be depressed. Quinine is preferable to chloroquine in these cases because of the uncertainty of parasite resistance to other drugs.

(2) Disintegration of the endothelial lining of the capillary vessels must be prevented. Corticosteroids inhibit many phenomena of the inflammatory process, though no explanation has been generally accepted. The inflammatory response is inhibited, whether the inciting agent is mechanical, toxic, or immunological. The value of glucocorticosteroids in reducing or preventing cerebral oedema is well established—in particular, by inhibiting the oedema by preserving the normal function of capillary endothelium. In this series Case 1 responded promptly to intravenous glucocorticosteroids.

(3) Capillary stasis must be prevented and the circulation in various organs, especially the brain, maintained. The first measure we took to prevent capillary sludging was to give low molecular weight dextran, which is valuable owing partly to its antithrombotic action and partly to its specific erythrocyte disaggregating effect, which we thought would prevent both stasis and the formation of haemagglutination thrombi in the cerebral microcirculation. We found, however, that low molecular weight dextran together with quinine were insufficient, and two patients died when this combination was given. Our next step to prevent capillary sludging was to give heparin, which has a well-known antithrombotic effect. Furthermore, some reports state that heparin has a specific antimalarial effect.[7] A prolonged clotting time can enhance cellular diapedesis through a damaged capillary wall (particularly when there is increased vascular congestion) and hence possibly there is a greater risk of cerebral haemorrhage. This is also well known in fatal cases of malignant tertian malaria, even when heparin has not been given. For instance, in Case 4 bleeding occurred in the perirenal capsule, not in the brain substance. Thus we believe that the benefit to be gained by giving heparin to prevent occlusion of cerebral capillaries by anticoagulation outweighs the risk of haemorrhage.

(4) Both cerebral oedema (Case 3) and pulmonary oedema (Case 4) may occur in a late stage of cerebral malaria. The doctor should remain on his guard even when the malaria parasites have disappeared from the patient's peripheral blood, the temperature has returned to normal,[8] and most signs and symptoms have subsided, as our Case 4 shows. Rigid maintenance of fluid and electrolyte balance is imperative, though clearly oedema in various organs can develop independently of fluid or electrolyte imbalance or both. When kidney function is not impaired a trial with urea dehydration can be life-saving.

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Therapeutic Conferences

Heart Failure—II

FROM THE DEPARTMENT OF THERAPEUTICS AND PHARMACOLOGY, ABERDEEN UNIVERSITY

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PROFESSOR MACGREGOR: We must now discuss the control of digoxin therapy. A patient with normal renal function and who is not losing potassium may tolerate 0·25 mg twice daily. If there is a pressing need 0·5 mg orally can be given six-hourly on the first day, or an intravenous dose may be given by slow injection. There are few occasions when this is necessary. In normal people half the digoxin given is excreted unchanged in the urine. For this reason, in patients with renal impairment the dosage should be reduced. The introduction of the 0·0625 mg tablet for use in paediatric and geriatric patients has been most useful.

DR. WOOD: A point to make is that intramuscular digoxin can be very painful. We must discuss the other cardiac glycosides.

DR. SHORT: Since the paediatric-geriatric tablet has been introduced I haven't used the other preparations.

DR. WOOD: But we musn't forget that ouabain is useful in

Appointments of Speakers

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