Review Article

MANAGEMENT OF CEREBRAL MALARIA IN THE YEAR 2001

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Introduction

Malaria affects about 5% of the world's population at any time and causes around 2.5 million deaths each year mainly in the tropics. Malaria is likely to remain a major killer in tropical countries till an effective vaccine and transmission control measures are developed. Almost all deaths are due to complicated *Plasmodium falciparum* infection which leads to multi-system disorder including diffuse cerebral encephalopathy (cerebral malaria). The case fatality in severe and cerebral malaria (CM) may be as high as 50% [1,2]. The delay in diagnosis, non-availability of expert and/or ICU facilities, poor socio-economic status of most malaria infected patients and the problem of resistance to chloroquine, pyrimethamine-sulphamethoxazole, mefloquine and even quinine in *P falciparum* are some of the reasons for sustained high mortality.

Prompt action is especially important for high-risk groups such as pregnant women, young children, and patients with pre-existing anaemia and their co-morbid conditions and visitors from non-endemic areas. The most important aspect is to entertain the possibility of malaria at an early stage under appropriate clinical setting and not to allow uncomplicated malaria to become complicated one.

Definition & Pathogenesis

Cerebral malaria in strict sense and for research purposes is defined as unrousable coma not attributable to any other cause in patients with proven *P falciparum* infection [3]. For treatment purposes however, any degree of impaired consciousness or any sign of cerebral dysfunction in appropriate setting should be treated as CM.

The pathogenesis is heterogenous and the neurological complications are often part of a multisystem dysfunction. The histopathological hallmark of cere-

bral malaria is engorgement of cerebral capillaries and venules with parasitised red blood cells (PRBCs) and non-parasitised RBCs (NPRBCs). The sequestration of red cells containing mature forms of parasites i.e. trophozoite and schizonts (meronts) in the microvasculature is thought to cause the major complications of falciparum malaria, particularly CM. Sequestration of red cells is due to either cytoadherence (interaction between PRBCs and vascular endothelium) caused by an increase in vessels expressing intracellular adhesive molecule-1 (ICAM-1), rosette formation (adherence of NPRBCs to PRBCs), agglutination (adherence of PRBCs to PRBCs) or decreased RBC deformability.

The clinical features of CM can be mimicked or aggravated by hypoglycaemia, lactic acidosis, drug toxicity, multi-organ dysfunction, febrile convulsions (in children), concomitant bacteraemia with or without systemic inflammatory response syndrome and algid malaria which are usual terminal events in these patients.

Clinical Features

The clinical picture of CM is quite varied and the alteration in sensorium may develop either gradually or manifest as persistent coma following a generalised convulsion. The usual clinical picture is that of a symmetrical upper motor neuron lesion. In some patients hypotonia and acute cerebellar ataxia may be encountered. There is usually diffuse symmetrical encephalopathy, sometimes with post reflex and bruxism. Severe headache, meningism, opisthotonus, a variety of neuro-ophthalmic posturing and abnormal respiratory patterns may also be encountered [4-6]. Seizures are seen in 20% to 50% of patients. EEG studies, especially in children, may sometimes demonstrate underlying status epilepticus even when it is not apparent clinically [6]. Pupils are symmetrical with normal pupillary, corneal, oculo-cephalic and oculo-vestibular reflexes. Photophobia, severe neck rigidity and

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papilloedema are almost never seen. Retinal haemorrhages are frequent and carry poor prognosis. Hypoglycaemia, raised intracranial pressure, severe anaemia, lactic acidosis, pulmonary edema, bleeding disorders and gram-negative septicemia are important complications.

Changes in behaviour may occur in the early stage, which may be followed by delirium, convulsions and coma. Thus, any non-immune adult with falciparum malaria showing a change in personality should be treated as cerebral malaria.

Diagnosis

A high index of suspicion, travel history and repeated blood smear examination for malarial parasite in all patients initially suspected to have the commonly prevalent febrile tropical diseases (which resemble malaria very closely) are the mainstay of diagnosis of *P falciparum* during its early uncomplicated stage. Although microscopic examination of the blood smear remains the routine and standard method, rapid immuno-chromatographic detection of circulating parasite antigen is likely to enter clinical practice [7]. Other relevant investigations including lumbar puncture etc. are mandatory in all cases to monitor the disease process and complications.

Treatment

Quinine based regimens:

All patients will need ICU care and cardiac monitoring. Due to widespread chloroquine resistance, therapy should begin with intravenous quinine in the doses of 20mg salt/kg in 5% dextrose over four hours, followed by 10 mg/kg in four hours, eight hourly provided the patient has not been given mefloquine or quinine in last 12 hours. An important point in the management of CM is to achieve therapeutic plasma concentrations of anti-malarial drugs as quickly as possible. This can be done by giving initial loading dose. The loading dose of quinine can safely be given even to the patients with renal or hepatic dysfunction in children [8]. We too have found it very safe and effective in Indian population [9]. The maximum mortality due to CM is during initial 48 hours and the therapeutic concentration can not be achieved by conventional therapy without a loading dose during this period. Patients should be on oral regime as soon as they are able to tolerate it to complete 5-7 days of quinine therapy. Doxycycline should also be administered in the dose of 3mg/kg once a day for 7 days to achieve better cure rates.

Hypoglycaemia is a real danger in CM that may be

worsened with quinine therapy. Hence, frequent glucose monitoring is mandatory.

Alternative Regimens :

Though there are no good data from our country, the fear of quinine resistance is genuine and artemisinin derivatives are now considered as the treatment of choice for quinine resistant *P falciparum*. A meta analysis of large number of randomised trials indicates that in adults, artemether did reduce mortality (by about one-fifth) but there was no convincing difference in children. The artemisinin derivatives should preferably be combined with mefloquine, tetracycline (4mg/kg QID for 7 days) or clindamycin to avoid late recrudescence which is common when these derivatives are used alone. Moreover, the present consensus is that antimalarials should not be used alone, but only in combination, to protect them from the emergence of resistance [9,10]. The most widely used regimen is intravenous/intramuscular artesunate (2.4mg/kg IV or IM stat followed by 1.2 mg/kg at 12 and 24 h and then daily for a total of 4 days) followed by mefloquine (1250 mg divided into two doses six hours apart). The doses of other artemisinin derivatives are as under :-

- (i) Artemether - 3.2mg/kg intramuscularly as loading dose followed by 1.6mg/kg once a day for 5 days.
- (ii) Arteether - 150mg intramuscular once a day for 3 days.

The various oral and suppository formulations of these drugs are being studied to determine the optimal dosage and schedule of administration for severe complicated malaria including CM at village/on the site levels i.e. where it is most needed. An oral fixed dose combination of artemether and lumefantrine (benflumetol) has been found to be quite effective and safe for uncomplicated acute *P falciparum* in our country and Thailand [11]. These drugs can also be administered through rectal route in the form of suppository [4].

Ancillary Treatment

Many ancillary treatments like monoclonal anti-TNF antibodies, steroids, desferrioxamine etc have been suggested and tried but none has been shown unequivocally to affect the outcome. Only antipyretics (acetaminophen), phenobarbital (in adults only) 3.5 mg/kg intramuscularly and exchange transfusion in complicated *P falciparum* with more than 10% parasitaemia have been supported by sufficient evidence to warrant their use [4,12,13].

Early detection and prompt treatment of pulmonary oedema, sepsis, renal failure, hepatic dysfunction,

anaemia, hypoglycaemia and cardiac toxicity of various antimalarials and meticulous nursing care of a comatose patient are other factors which will decrease the overall mortality and morbidity due to CM.

Common errors in management as mentioned below should be avoided :

- i) Omission of loading dose of quinine.
- ii) Bolus or push intravenous quinine.
- iii) Administration of steroids.
- iv) Administration of mannitol [3].

Mannitol administration may result in hypervolemia, pulmonary edema, oliguria, anuria, azotemia, hyperosmolality, hypernatraemia, and hypokalaemia, hence it should be avoided [3].

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