# CEREBRAL MALARIA

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## INTRODUCTION

Malaria is one of the most infectious diseases of man and is perhaps responsible for more morbidity and economic losses than any other disease alone. It is produced by a parasite of class Sporozoa and genus Plasmodium. It has four species namely Vivax, Ovale, Falciparum, and Malariae. Its vector is a female Anopheles mosquito, while its vertebrate host is man. Out of the four species of Plasmodium, falciparum is the most aggressive and produces a malignant disease characterized by high grade fever, extensive haemolysis, severe anaemia, jaundice and visceromegaly. Besides these, Plasmodium falciparum has some special presentations like Black Water Fever, Transplacental Transmission and Cerebral Malaria.

According to a World Health Organization report regarding World Malaria Situation in 1990, the global incidence of malaria is 120 million cases each year, out of which more than a million die annually.[1] Majority of the victims are children and cerebral malaria is the main culprit.[2] Many workers like Phillips and Solmon[3] believe that cerebral malaria is invariably lethal if left untreated. This is an aggressive disease with a very rapid rate of progression, and many young children die even before they can reach any medical facility.[4] The scenario of cerebral malaria is even worse in the underprivileged and neglected conditions like ours. The clinical outcome of cerebral malaria is directly related to the optimacity of medical facilities and as Endeshaw and co-workers[5] have noted, the morbidity and mortality of cerebral malaria is increased in suboptimal clinical conditions.

## PATHOGENESIS

The pathogenesis of cerebral malaria was rather poorly understood until recently, when the following different mechanisms were described independently.

1. Red blood cells, parasitized with Plasmodium falciparum, are selectively sequestrated into the microvasculature of certain tissues. This differential sequestration of red blood cells is maximum in the brain tissue, and more so in the cerebrum and cerebellum.[6]

2. The parasitized red blood cells develop knob like projections on their surface. These protrusions retard the velocity of red blood cells in the microvasculature of the affected tissues. As a result margination of the affected cells takes place.[7] Owing to the margination of these cells, velocity of the blood flow decreases causing distal ischaemia and hypoxemia.

3. The parasitized red blood cells on coming in contact with the vascular endothelial cells, induce adhesiveness in these endothelial cells.[8] As a result there is

margination and adherence of the parasitized red blood cells to the endothelial cells, thus further reducing the blood flow in the microvasculature of the affected tissues. This further enhances the tissue hypoxia and ischaemia.

4. The parasitized red blood cells express on their surface membrane certain proteins, called "rosettins". These rosettins are derived from P. falciparum. On the other hand, non infected red blood cells have some carbohydrate moieties on their surface, which make strong lectin like bindings with these rosettins. As a result rosette formation occurs, causing clumping of red blood cells together and diminishing blood flow through the microvasculature of the brain tissue, worsening the ischaemia and hypoxemia. It is believed that rosetting plays a vital role in the pathogenesis of severe falciparum malaria disease.[9]

The tendency of rosetting is altered by many factors like A, B, O blood groups and haemoglobin structure. The rosettes of red blood cells with blood group A and B are very strong and large, thus predisposing to severe disease. On the other hand, red blood cells from individuals with blood groups O, haemoglobin E, Alpha and Beta thalassaemia traits and Sickle cell trait make weak and small rosettes, thus protecting against severe attacks of cerebral malaria.

5. Patients suffering from P. falciparum malaria have been observed to have an abnormal circulatory control. They suffer from orthostatic hypotension and bradycardia.[10] Both these factors reduce blood flow through the microvasculature of the brain tissue, thus potentiating the hypoxic and thrombotic influences of P. falciparum malaria.

6. Human body responds to the antigenic stimulation of malaria by a generalized inflammatory response.[11] As a result there is increased release of histamine and kinins, leading to excessive vascular permeability and endothelial cell damage. This along with extravasation of blood and plasma leads to oedema and swelling of brain tissue producing the various cerebral herniation syndromes,[11] and the different neurological manifestations of the disease.

7. The other major host response is hyperactivity of the sympathetic nervous system,[11] giving rise to vasoconstriction of the splanchnic vessels, leading to the following consequences.

(A) Vasoconstriction occurring in the liver causes increased portal pressure and tissue hypoxia resulting in passive hepatic congestion and centrolobular necrosis.

(B) Vasoconstriction in mesenteric arteries causes gastrointestinal symptoms like nausea, vomiting and diarrhoea.

(C) Vasoconstriction in the kidneys leads to reduced renal blood flow and, therefore, reduces urine output and elevates blood urea.

Putting all these different proved mechanisms together, paints a rather clearer picture of the pathogenesis of cerebral malaria, and its systemic associations.

## CLINICAL FEATURES

The cardinal feature of cerebral malaria is coma.[12] The presenting features of cerebral malaria include fever, vomiting, pallor, jaundice, dehydration, shock, headache, lethargy, encephalitic behaviour, focal or generalized seizures and change of sensorium rapidly progressing to coma. Spasticity is common. Patients may exhibit decorticate or decerebrate posture. Opisthotonus is manifested in extreme cases. Respiration may be Cheyne-Stroke, ataxic, or central hyperventilation type. Respiratory arrest is a common cause of death. Infancy, gross anaemia, prolonged history (more than 5 days), witnessed seizures, deep coma, hypoglycemia, and decerebration are bad prognostic features.[12,13]

The WHO criteria for the diagnosis of cerebral malaria include fever, asexual falciparum parasitaemia and unrousable coma[14] lasting for more than 30 minutes. Unrousable coma of upto 30 minutes duration can occur with febrile fits associated with malaria.[15] This is a fairly strict criteria and probably necessary to be adopted as a uniform research policy, but in practice, the detection of malaria parasite in every case is a recognised difficulty,[3] and many workers very rightly feel that in clinically suspected cases of cerebral malaria, failure to identify P. falciparum may seriously delay treatment and lead to undesirable consequences.[16]

Clinical examination may reveal signs of meningeal irritation. Hepatomegaly and splenomegaly are found in 30-40% patients.[13] Retinal haemorrhages are an uncommon finding on fundoscopic examination.[13]

## DIAGNOSIS

Clinical diagnosis of cerebral malaria is usually difficult and requires a low threshold of suspicion for timely recognition of this aggressive disease process. In endemic areas, cerebral malaria must be considered in the differential diagnosis of all patients presenting with an encephalitic or meningitic profile. A daily blood smear for malaria parasite should, therefore, be included in the management plan of all such patients.

Cerebrospinal fluid examination is mandatory to rule out the possibility of meningitis. In cerebral malaria the CSF is usually normal, but raised CSF pressures, however, have often been reported.[13,17] Relevant investigations should be carried out to exclude other causes of coma. Blood glucose level should be carefully estimated as pretreatment hypoglycemia is a common complication of severe falciparum malaria.[11,18] The etiology of this hypoglycemia is uncertain, but may be explained by poor intake, vomiting, parasite utilization of glucose and impaired host hepatic gluconeogenesis.

## TREATMENT

The patients of cerebral malaria respond rather briskly to antimalarial therapy if seen earlier, but the outcome is equally gloomy in late attenders. Chloroquine and quinine have comparable results if the organism is sensitive to chloroquine.[19] Chloroquine is recommended both as intermittent therapy (5mg/Kg/dose twice daily), and as continuous infusion (10mg/Kg first dose, then 15mg/Kg/24 hours for three days).[20]

Owing to the increasing resistance to chloroquine, quinine therapy is becoming the gold standard in endemic areas, and is recommended by WHO since 1986. To clear initial parasitaemia, a bolus dose of quinine (20mg/Kg) is given stat, followed by 10mg/Kg twice daily for 3 to 5 days. The bolus dose of quinine should be used cautiously owing to its potential side effects.[21] Non-judicious and indiscriminate use of this vital drug is to be discouraged, to avoid development of resistance which has recently been reported.[22]

Anticonvulsant therapy is usually required. Phenobarbitone offers a cheap and effective option.[23] Diazepam is effective for controlling current fits. Due to the danger of apnoea, quick and frequent use of diazepam should be avoided.

The use of steroids had been controversial once, but now it is uniformally considered as ineffective,[24] and even harmful.[25]

The syndrome of inappropriate antidiuretic hormone release can be a dangerous association of cerebral malaria. Serum electrolytes should be monitored carefully, and intravenous fluids should be cautiously administered. A restricted fluid intake schedule (ie 60mls/Kg/24hours) saves subsequent botheration.

## MORBIDITY AND MORTALITY

Cerebral malaria is believed to be a serious presentation of P. flaciparum disease, but the general outcome of patients receiving timely treatment is usually favourable. Depending upon the facilities, working conditions and accuracy of diagnosis, the figures for mortality differ from study to study and range from 8%-20%.[2,12,13]

Contrary to the previous belief, total recovery from cerebral malaria is no more the rule. Neurological sequelae are increasingly being reported with a range incidence of 6%-22%.[13,26,27] Hemiplegia stands as the commonest neurological deficit.

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