

Clinical Profile of Cerebral Malaria at a Secondary Care Hospital

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ABSTRACT

Introduction: Cerebral malaria (CM) is one of the most common causes for non-traumatic encephalopathy in the world. It affects both the urban and rural population. It is a challenge to treat these patients in a resource limited setting; where majority of these cases present. **Materials and Methods:** This was a prospective study carried out from September 2005 to December 2006 at Jiwan Jyoti Christian Hospital in Eastern Uttar Pradesh in India. This is a secondary level care with limited resources. We studied the clinical profile, treatment and outcome of all the patients above the age of 14 years diagnosed with CM. **Results:** There were a total of 53 patients with CM of which 38 (71.7%) of them were females. Among them, 35 (66%) patients were less than 30 years of age. The clinical features noted were seizure (39.62%), anemia (84.9%), icterus (16.98%), hypotension (13.2%), bleeding (3.7%), hepatomegaly (5.66%), splenomegaly (5.66%), non-cardiogenic pulmonary edema (16.98%) and renal dysfunction (37.36%). Co-infection with *Plasmodium vivax* was present in 13 (24.53%) of them. Treatment received included artesunin compounds or quinine. Median time of defervescence was 2 (interquartile range 1-3). Complete recovery was achieved in 43 (81%) of them. Two (3.7%) of them died. **Conclusion:** CM, once considered to be a fatal disease has shown remarkable improvement in the outcome with the wide availability of artesunin and quinine components. To combat the malaria burden, physicians in resource limited setting should be well trained to manage these patients especially in the endemic areas. The key to management is early diagnosis and initiation of treatment based on a high index of suspicion. Anticipation and early recognition of the various complications are crucial.

Keywords: Cerebral malaria, clinical profile, secondary care hospital

Introduction

Malaria is one of the most common parasitic infections in the developing countries and cerebral malaria (CM) is one of the most common causes for non-traumatic encephalopathy in the world. Malaria is caused by five species of *Plasmodium* namely *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium knowlesi*. Most of the cases of CM are caused by *P. falciparum*. However, they are increasing reports of complicated malaria by other species as well.^[1,2]

Clinical presentation of malaria varies from uncomplicated acute febrile illness to a severe form of malaria when infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. The manifestations of severe malaria include CM, severe anemia, hemoglobinuria due to hemolysis, acute respiratory distress syndrome,

abnormalities in blood coagulation, hypotension, acute kidney injury, hyperparasitemia (more than 5% of the red blood cells (RBCs) infected by malarial parasites), metabolic acidosis and hypoglycemia. Severe malaria is a medical emergency and should be treated urgently and aggressively.^[3]

In the Indian scenario, these patients would be treated by the primary and the secondary care physicians. For the same reason, these physicians should be aware of the complications, so that earlier and effective treatment can be initiated and patients who need a referral to a tertiary care can also be identified.

Materials and Methods

This was a prospective study done from September 2005 to December 2006 at Jiwan Jyoti Christian Hospital in Eastern Uttar Pradesh in India. This is a secondary level care with limited resources. All the patients above the age of 14 years diagnosed with CM were included in the study. CM was defined as a clinical syndrome of coma (inability to localize a painful stimulus) at

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least 1 hour after termination of a seizure or correction of hypoglycemia, detection of asexual forms of *falciparum* malarial parasite on peripheral blood smear and exclusion of other causes of encephalopathy.^[2] We further studied the clinical profile, treatment and outcome of these patients.

Results

There were a total of 53 patients with CM of which 38 (71.7%) of them were females. Among them 35 (66%) patients were less than 30 years of age [Figure 1] all of them had presented with fever and altered sensorium with documented malarial parasite on the peripheral blood film. Twenty one (39.62%) of them had a history of seizures. Other clinical features [Figure 2] noted were pallor (35%), icterus (16.98%), hypotension (13.2%), bleeding (3.7%), hepatomegaly (5.66%) and splenomegaly (5.66%). Non cardiogenic pulmonary edema was present in 9 (16.98%) of them.

Majority (84.9%) of the patients had anemia. Hypoglycemia was documented in only one patient. Deranged renal function was noted in 20 (37.36%) of them. These patients were managed conservatively. All the patients had documentation of *P. falciparum* on the peripheral blood film. Co-infection with *Plasmodium vivax* was present in 13 (24.53%) of them.

Treatment received included artesunin compounds (artesunate in 37 and arteether in 3), quinine (9) and quinine – doxycycline combination therapy (2). In view of clinical failure 3 of them were switched over from artesunate to quinine.

Median time of defervescence was 2 (interquartile range 1-3). Complete recovery was achieved in 43 (81%) of them. Two (3.7%) of them died. Others included patients who were referred to higher center and those who left the hospital against medical advice.

Discussion

CM is a diffuse encephalopathy in which focal neurological signs are relatively unusual. It is often accompanied by multisystem

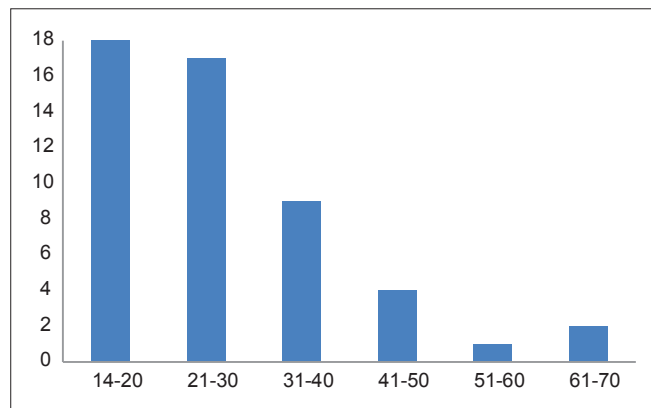


Figure 1: Age distribution of patients with cerebral malaria

dysfunction. CM is defined as severe *P. falciparum* malaria with cerebral manifestations, usually coma (Glasgow coma scale < 11, Blantyre coma scale < 3). Malaria with coma persisting for > 30 min after a seizure is also considered to be CM.^[4]

The 2010 revised criteria for severe malaria are the presence of one or more of the following: Prostration, impaired consciousness, failure to feed, respiratory distress (“air hunger”), multiple seizures (more than two episodes in 24 h), circulatory collapse, pulmonary edema (on radiological imaging), abnormal spontaneous bleeding, jaundice, hemoglobinuria, severe anemia, hypoglycemia, acidosis, renal impairment, hyperlactatemia, and hyperparasitemia.^[4]

According to the latest World Health Organization (WHO) estimates, there were about 219 million cases of malaria in 2010 and an estimated 660,000 deaths. Africa is the most affected continent: About 90% of all malaria deaths occur there.^[5]

Among the 53 patients with CM, 71.7% were females and 66% were less than 30 years of age. However Wasnik *et al.* noted a higher incidence in males (75%) most of whom were in the age group of 21-30 years of age.^[6] Seizure was the presenting symptom in 39.62% patients. Seizures are a prominent feature in CM and repeated seizures have been associated with poor outcome. Children have a higher incidence of seizures. Camara *et al.* noted seizures in 52.5% of the children with *P. falciparum*.^[7]

Patel noted that 46.8% of the patients with *falciparum* malaria had anemia whereas Wasnik *et al.* noted that 65% of the cases had anemia.^[6,8] In our cohort 84.9% had anemia. The higher incidence could have been due to underlying anemia prior to the infection. Studies from Ghana noted an incidence of 66.2% among the children.^[9]

The causes for anemia in CM patients are obligatory destruction of RBCs containing parasites at merogony, accelerated destruction of non-parasitized RBCs and bone marrow dysfunction.

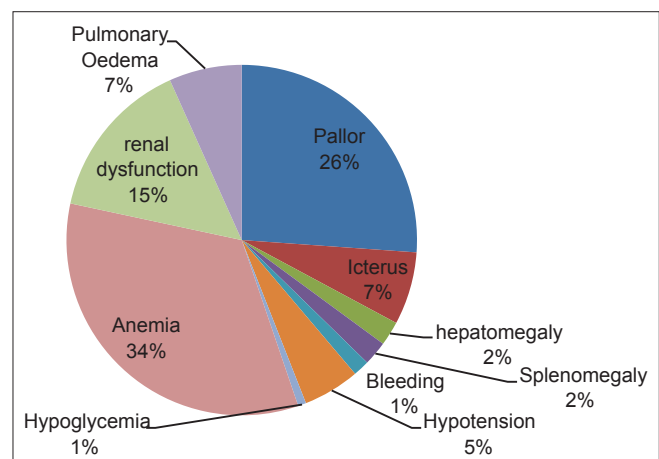


Figure 2: Clinical features of patients with malaria

Hypoglycemia in CM patients are due to increased peripheral requirement of glucose consequent upon anaerobic glycolysis, increased metabolic demands of febrile illness, obligatory demand of parasites, failure of hepatic gluconeogenesis and glycogenolysis (parasites consume up to 70 times as much glucose as uninfected cells). It is compounded by the stimulation of insulin secretion from pancreatic beta cells by quinine. Hypoglycemia was present only in one of our cases. Blood sugars of all the patients in the present study were closely monitored and glucose supplementation was given. In a previous study the incidence of hypoglycemia was 6.38%.^[8]

Renal dysfunction causes morbidity in these patients. Biochemical evidence of renal dysfunction was noted in 37.6% patients. None of them required hemodialysis and were managed conservatively with diuretics and fluids. It is comparable to the previous studies where the incidence was 32.5%.^[6] Out of 526 cases of CM reported from Rourkela, in Sundargarh district of Orissa state, 28.9% had acute renal failure (ARF).^[10] Mortality in this series was particularly high (59%) specifically in those with multiorgan failure. The effect of associated ARF on mortality in CM patients indicated, mortality was as high as 39.5% when associated with ARF, while it was only 13.9% when unassociated with ARF.

Metabolic acidosis is a known complication of malaria. Hyperventilation (Kussmaul breathing) with a clear chest on auscultation suggests metabolic acidosis. At our center since there was no facility for estimation of blood gases, we made a clinical diagnosis based on this and was initiated on soda bicarbonate infusion and fluids. Clinical improvement as indicated by normal respiratory rate guided us in our management.

In our study, 16.9% patients had non cardiogenic pulmonary edema. Unavailability of mechanical ventilation in three of the patients attributed to mortality. Rest of the patients had responded to diuretics. Case fatality rate is very high in these patients and they should be referred to a facility where mechanical ventilation and intensive care is available.

Antimalarial drugs are the only interventions that unequivocally reduce mortality in patients with malaria. The cinchoids (quinine and quinidine) and artemisinin compounds are most commonly used. The World Health Organization now recommends using intravenous artesunate in preference to quinine for the treatment of severe *P. falciparum* malaria in adults.^[11] Combination therapy with doxycycline has been recommended in the severe malaria cases.

The artemisinins components available for treatment of malaria are artemether, arteether and artesunate. These are derivatives of Chinese drug qinghaosou. In a large open label, randomized trial of Asian adults with severe malaria, artesunate significantly reduced mortality by 34.7%.^[12] Majority (75.47%) of our patients were treated with artesunate components. Out of these except for 3 patients rest of them had responded to artesunate. Artesunate

was replaced by quinine in these patients to which they had responded. Combination therapy of quinine with doxycycline was used in only 3 patients. Quinine was given under cardiac monitoring. However, no cardiac complications were noted in any of these patients.

Mortality rate was 3.7% in this study. Lon *et al.* noted a mortality rate of 35% among CM cases.^[13] Wasnik *et al.* noted that the cause of death were ARF, metabolic acidosis, aspiration pneumonia and circulatory failure.^[6] Case fatality rates in the other studies from Africa have shown a high mortality rate of 13-21%.^[14,15]

Primary care physicians should be able to diagnose CM from the clinical presentation, which should be supported by detection of *P. falciparum* or in some cases the other species of malaria on the peripheral blood film. Once a diagnosis of malaria is made, they should anticipate the various complications. Artesunate components as combination therapy are the drug of choice as per WHO recommendations and can be easily administered with hardly any side effects.^[11] Non cardiogenic pulmonary edema needing ventilator care and renal failure needing dialysis should be referred to a higher facility.

Conclusion

CM once considered a fatal disease has shown remarkable improvement in the outcome with the wide availability of artesunate components. Most of the complications of severe *falciparum* malaria including CM can be managed by a primary care physician. Considering the health system in our country if primary care physicians can manage these patients, it will go a long way in reducing the morbidity and mortality of these cases.

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