

Burden of Cerebral Malaria in Central India (2004–2007)

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Abstract. A study on the clinicoepidemiology of cerebral malaria (CM) and mild malaria (MM) among adults and children attending NSCB medical college hospital Jabalpur and civil hospital Maihar, Satna, in central India was undertaken. Of 1,633 patients, 401 were *Plasmodium falciparum* and 18 *P. vivax*. Of 401, 199 CM patients and 112 MM patients were enrolled. Severe complications among CM patients were jaundice (26%), acute renal failure (22%), respiratory distress (22%), severe malaria anemia (18%), hypotension (17%), hepatic encephalopathy (7.0%), and hematuria (5%). Among CM cases, seizures and severe malaria anemia were significantly higher in children ($P < 0.0001$) compared with adults, whereas jaundice ($P < 0.0025$), acute renal failure ($P < 0.0001$), and hematuria ($P \leq 0.05$) were significantly higher among adults. Mortality was high among adults with multiple organ failures. Overall case fatality rate was 21%. Neurologic sequelae at discharge from the hospital were 3%, whereas at follow-up, only 1% had persistent neurologic sequelae.

INTRODUCTION

Malaria is a disease of global importance that results in 300–500 million cases annually. Forty percent of the world population lives in malaria-endemic areas,¹ and 1.5–2 million deaths, mostly children (< 5 years), occur annually.² *Plasmodium falciparum* may infect humans at conception through adulthood.³ Approximately 2.4 million malaria cases are reported annually from South Asia, of which 75% are reported in India alone.⁴ *P. falciparum* infections have dramatically increased in central India in recent years.^{5,6}

Cerebral malaria (CM) is the most common complication of *P. falciparum* infection, which may result in severe complications,^{3,7,8} including long-term neurologic impairment,^{9,10} multi-organ failures,^{11,12} and high mortality rates¹³ in the absence of prompt diagnosis and appropriate treatment.¹⁴ Increasing drug resistance against *P. falciparum* contributes to further increases in malaria morbidity. There are very few scientific reports from India describing clinical features and neurologic sequelae,¹¹ mainly because of poor infrastructure and inadequate diagnostic facilities.¹³

The main goal of this clinico-epidemiologic study was to explore the epidemiology of CM and mild malaria (MM) in patients attending a primary and tertiary hospital in central India and to comprehensively document on morbidity and mortality associated with *P. falciparum* infections. Patients were followed over a 6-month period and screened for the presence of long-term neurologic sequelae, if any. This prospective study is part of a National Institutes of Health (NIH)-sponsored study on “Cerebral malaria associated neurological disorders in central India” in collaboration with The Center for Disease

Control (CDC) and Morehouse School of Medicine (MSM) in Atlanta, Georgia.

MATERIALS AND METHODS

Study sites. A prospective study was initiated from October 2004 to September 2007 at Nethaji Subhash Chandra Bose (NSCB) Medical College Jabalpur, and Civil Hospital (primary hospital) in Maihar, Satna District, Madhya Pradesh, Central India (Figure 1). The National Institute of Malaria Research (NIMR) field station at Jabalpur established a malaria clinic at the Department of Medicine, Medical College Hospital, and Civil Hospital at Maihar, where all blood smears of suspected malaria cases were prepared and examined for malaria parasites. All unconscious patients admitted to the NSCB Medical College hospital were also referred to the NIMR clinic for malaria diagnosis.

Study subjects. Patients admitted to the medicine and pediatric units of Medical College Hospital, Jabalpur, and Civil Hospital Maihar between 2004 and 2007 were enrolled after obtaining informed consent to those meeting the WHO criteria for cerebral malaria.¹⁵ CM was defined as unrousable coma (a non-purposeful response or no response to a painful stimulus) in a patient with evidence of peripheral parasitemia (asexual parasites) when other possible causes of coma (i.e., hypoglycemia, meningitis, encephalitis) were excluded. Detailed clinical and neurologic examination was conducted by the attending physician at the time of admission and daily thereafter, until the time of discharge. MM was defined as patients who had fever with *P. falciparum* parasitemia (< 25,000 parasites/ μ L) of blood with no evidence of impaired consciousness, seizures, or other complications.

On admission, a detailed clinical history was obtained. Informed consent and human experimentation guidelines of the National Institutes of Health (NIH, USA) were followed. In this study, all the enrolled CM and MM patients were dual

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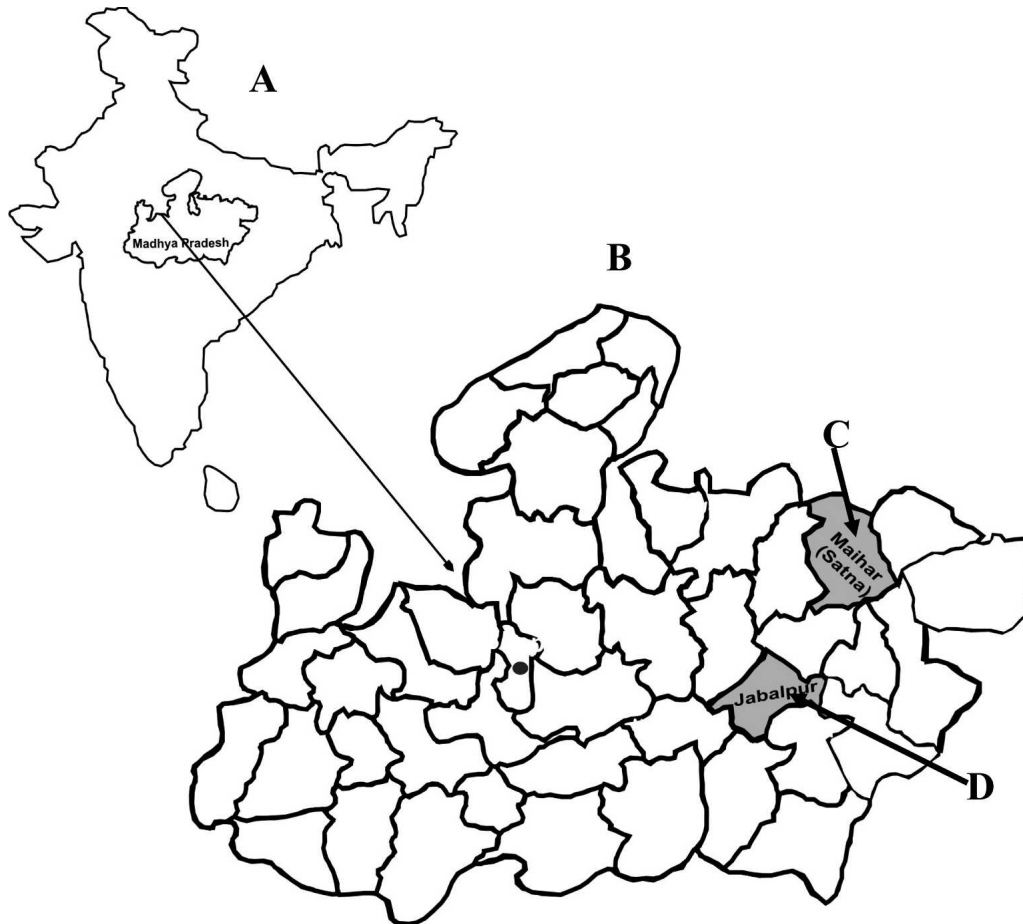


FIGURE 1. **A**, Map of India showing Madhya Pradesh state. **B**, Madhya Pradesh state showing study site. **C**, Civil Hospital, Maihar district, Satna. **D**, NSCB Medical College, district, Jabalpur.

checked for *falciparum* malaria by microscopy and with a *P. falciparum*-specific HRP-2-based rapid diagnostic test ParaHIT *f*.¹⁶ Peripheral smears were examined by an experienced microscopist. Blood films were labeled as negative if there were no asexual forms of *P. falciparum* in 100 high power fields of a thick film. Relevant clinical data and information (duration of coma, seizures, occurrence of systemic complications, date of discharge from the hospital, etc.) were recorded for each patient from physicians records.

The complete blood cell count was done with an automated cell counter (diatron; Arcus, Wien, Austria). All patients were treated by intravenous/oral quinine, and specific syndromes were managed according to WHO guidelines. Supportive care such as intravenous fluids, analgesic, sedatives, anti-convulsants, and anti-pyretics were given to all the patients. Patients with severe anemia were given blood transfusion when needed. Pregnant women were not enrolled in the study. Follow-ups of CM patients were conducted 6 months after discharge from the hospital.

Clinical evaluation. Complications were indicated by the following criteria: acute renal failure (ARF), serum creatinine > 3 mg% and urine output < 400 mL/24 h for adult and < 12 mL/kg/24 h for children; severe malaria anemia (SMA), hemoglobin < 5 g/dL; moderate malaria anemia, 5–7.9 g/dL; mild malaria anemia, 8–10.9 g/dL; hypoglycemia, blood glucose level < 40 mg/dL; jaundice, serum bilirubin > 3 mg/dL;

hypotension, systolic blood pressure (BP) < 80 mm of Hg for adults and < 50 mm of Hg for children (< 5 years); leukocytosis, peripheral total leukocyte count > 12,000/mm³; leukopenia, peripheral total leukocyte count < 5,000/mm³; neutropenia, peripheral platelets count < 80,000/mm³. The term neurologic sequelae was applied to the persistence of neurologic manifestations at the time of discharge.

Sickling and G6PD deficiency evaluation. Cellulose acetate paper electrophoresis was used to detect sickle cell and hemoglobin status,¹⁷ and the DCIP discoloration method was used for G6PD deficiency.¹⁸ This study was approved by the ethics committee of the NIMR, RMRC, CDC, and MSM.

Data analysis. Data was entered into a Microsoft Excel (Redmond, WA) worksheet. Age was coded in a categorical variable “Age Group” before data analysis. Data analysis was done using computer software Epi Info 3.3.2 (CDC, Atlanta, GA) and STATA-8.2 (Statacorp., College Station, TX). χ^2 analysis was used for a 2 × 2 contingency table for comparison of the categorical data, and Student *t* tests were used for comparison between the two means.

RESULTS

Of 1,633 symptomatic patients with suspected malaria, 419 (25.6%) were positive for malaria. Of these, 401 were *P. falciparum* (96%) and 18 (4%) were *P. vivax* infections. Of 401

TABLE 1
Summary of features of cerebral malaria patients admitted in Medical College Jabalpur and Civil Hospital Maihar, District Satna

Complications	Adults (N = 120)			Children (N = 79)			Relative risk (95% CI)	P
	N	Present	Percent	N	Present	Percent		
Jaundice	120	40	33.33	79	11	13.92	2.39 (1.31–4.38)	< 0.0025
Hepatic encephalopathy	120	12	10.00	79	2	2.53	3.95 (0.91–17.18)	≤ 0.05
Hematuria*	119	9	7.56	79	1	1.27	5.97 (0.77–46.24)	≤ 0.05
Hypotension†	119	20	16.81	74	13	17.57	0.96 (0.51–1.81)	> 0.05
Acute renal failure* (ARF)	119	40	33.61	79	4	5.06	6.64 (2.47–17.82)	< 0.0001
Respiratory distress‡	117	28	23.93	73	14	19.18	1.25 (0.70–2.21)	> 0.05
Seizures§	118	30	25.42	79	49	62.02	0.41 (0.29–0.58)	< 0.0001
Severe malaria anemia (SMA)¶	110	8	7.27	67	24	35.82	0.20 (0.1–0.43)	< 0.0001
Moderate malaria anemia**	110	42	38.18	65	28	43.08	0.89 (0.61–1.28)	> 0.05
Mild malaria anemia**	110	47	42.73	65	11	16.92	2.52 (1.41–4.51)	< 0.0005

* One missing observations.
 † Six missing observations.
 ‡ Nine missing observations.
 § Two missing observations.
 ¶ Twenty-two missing observations.
 ** Twenty-four missing observations.

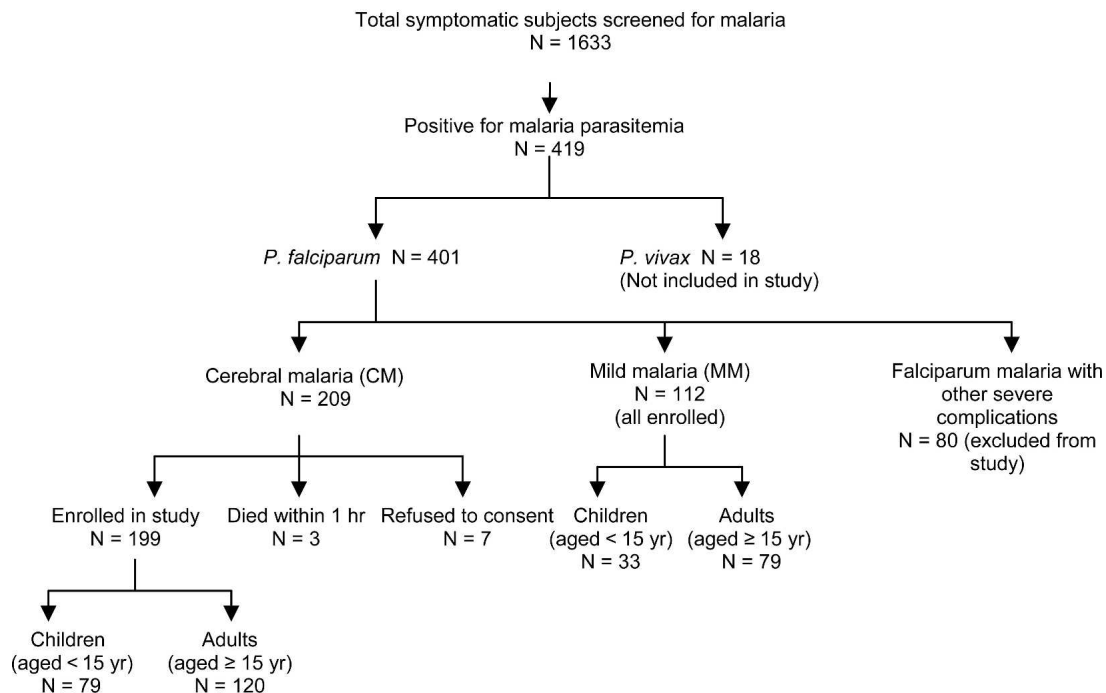
P. falciparum, CM was recorded in 209 patients (52%), severe malaria with other complications in 80 subjects (not included in the study as per the protocol), and mild malaria in 112 cases. Only 199 CM cases were enrolled in this study because 3 patients died within an hour after admission, whereas 7 others did not give consent (Flow Chart). All the 199 CM cases (135 male and 64 female; 1:0.5) and 112 MM patients (68 male and 44 female; 1:0.65) in this study originated from rural areas of low socio-economic status. Seventy-nine (40%) of 199 CM patients were children (age, < 15 years), whereas 33 (29%) of 112 MM were children. The duration of illness (fever) before hospitalization was similar (mean = 6 days; range, 1–15 days) in both adults and children with CM and MM. Among CM patients, only 10% had a 1- to 2-day history of fever before falling into deep coma and convulsions, whereas 20% of comatose patients were afebrile on admission. Ninety-nine per-

cent of patients were unconscious at the time of admission. Only two women, one of whom died, were disoriented at the time of admission but fell into a coma afterward.

The most common symptoms at presentation were fever (80%), seizures (40%), vomiting (24%), headache (16%), hepatosplenomegaly (8%), and splenomegaly (4%). Other severe complications included jaundice (26%), ARF (22%), respiratory distress (22%), SMA (18%), hypotension (17%), hepatic encephalopathy (7%), hypoglycemia (4%), and hematuria (5%) (Table 1). Also, 19% of patients had leukocytosis, 12% had leukopenia, and 27% had thrombocytopenia.

Seizures and SMA were significantly higher in children ($P < 0.0001$) compared with adults, whereas jaundice ($P < 0.0025$), ARF ($P < 0.0001$), and hematuria ($P \leq 0.05$) were significantly higher in adults. Respiratory distress was relatively higher in adult CM patients, but this difference was not

Classification of enrolled subjects



Flow Chart

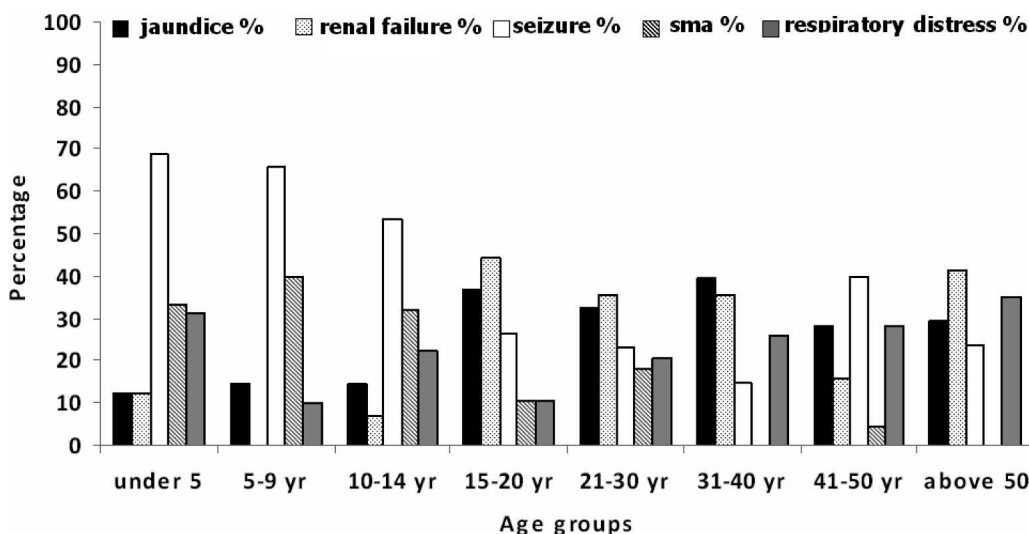


FIGURE 2. Complications by age group among CM patients admitted in Medical College, Jabalpur, and Civil Hospital Maihar, Satna.

statistically significant (Table 1). The distribution of CM-associated severe complications in different age intervals is shown in Figure 2. Seven percent of adult and 23% of children received blood transfusions.

Neurologic features are shown in Table 2. Acute psychosis, cerebellar signs, and nystagmus were present at the time of discharge from the hospital. Additionally, two patients who recovered with neurologic sequelae such as “amblyopia” and “cerebral diplegia” showed no improvement in condition at follow-up after 6 months.

Other manifestations observed in CM patients were gastrointestinal bleeding/disseminated intravascular coagulation (3.5%), rashes/allergic erythremia (1%), gangrene of pedal part (1%), and adult respiratory distress syndrome (1%).

Forty-one CM patients died, 29 of whom were adults (70.73%). Mortality was especially high (40%) among subjects with multi-organ failure. Adults had a higher mortality rate because of the presence of multiple complications (relative risk [RR], 1.88; 95% CI, 1.01–3.48). Only 10.6% of the CM patients who had no associated complications died compared with 40% of those who had multiple organ dysfunctions (MODs).

Hospital records showed that 44% of the fatal cases died within the first 24 hours of hospitalization, of which three deaths (1.5%) occurred within the first 6 hours. Another 15% died within 48 hours, 24% died in 72 hours, and a further 17% died after 72 hours of hospitalization. Self-medication with anti-pyretic or anti-malarial drugs was common. Stratification showed that > 70% were referred cases from nearby districts and 29% were referred from peripheral areas of Jabalpur.

The recovery pattern showed that, among adults, coma persisted for 24 hours in 38% and > 96 hours in only 7% patients. Among the pediatric cases, one half of the CM cases (50%) recovered within 24 hours, and coma persisted for > 72 hours in only 7% (Figure 3). Of 199, 139 (70%) were discharged from the hospital after complete recovery, 21% died, 9.5% left against medical advice, and 0.5% left without informing the attending physician. Among 57 CM cases (34 adult, 23 children) that were followed up 6 months later, 3 adults and 5 children died while at home. Five (two adult and three children) of eight deaths that occurred between admission

and follow-up were among those who left the hospital against medical advise. The duration time until death (mean ± SD) for children was 7.4 ± 6.2 days and for adults was 43.3 ± 28.8 days. Blood smear examination of follow-up cases also showed one positive case of *P. falciparum* and another of *P. vivax*.

There was no difference in symptoms (fever, vomiting, headache, hepatosplenomegaly, splenomegaly, and mild anemia) when MM cases were compared with CM patients (Table 1). However, geometric mean parasite density (3,861.62 ± 7.71 versus 1,890.66 ± 3.06), number of days in the hospital (6.03 ± 3.65 versus 3.52 ± 1.46), and moderate anemia (40% versus 27%) were significantly higher in CM compared with MM. Complications associated with CM were completely absent in MM cases. G6PD deficiency was found in only two CM and one MM patients, whereas sickle cell hemoglobin was absent in both CM and MM patients.

DISCUSSION

Falciparum malaria is associated with life-threatening complications in both children¹⁹ and adults.^{11,13} However, the severity and clinical presentation of *P. falciparum* depend on the age, intensity of transmission, and immunity of the patient.¹² Furthermore, there are important differences between the pattern of disease in children compared with adults.^{7,20,21} Thus, defining the clinical spectrum of malaria in different age groups is necessary for studies conducted in areas of different malaria endemicity and transmission dynamics. CM was a

TABLE 2
Summary of neurologic sequelae of cerebral malaria patients admitted in Medical College Jabalpur and Civil Hospital Maihar, District Satna

Type of complication	Adults (N = 120)		Children (N = 79)	
	Present	Percent	Present	Percent
Acute psychosis	Nil	0.0	1	1.27
Cerebellar signs	1	0.83	1	1.27
Nystagmus third nerve	1	0.83	Nil	0.0
Amblyopia	Nil	0.0	1	1.27
Cerebral diplegia	Nil	0.0	1	1.27

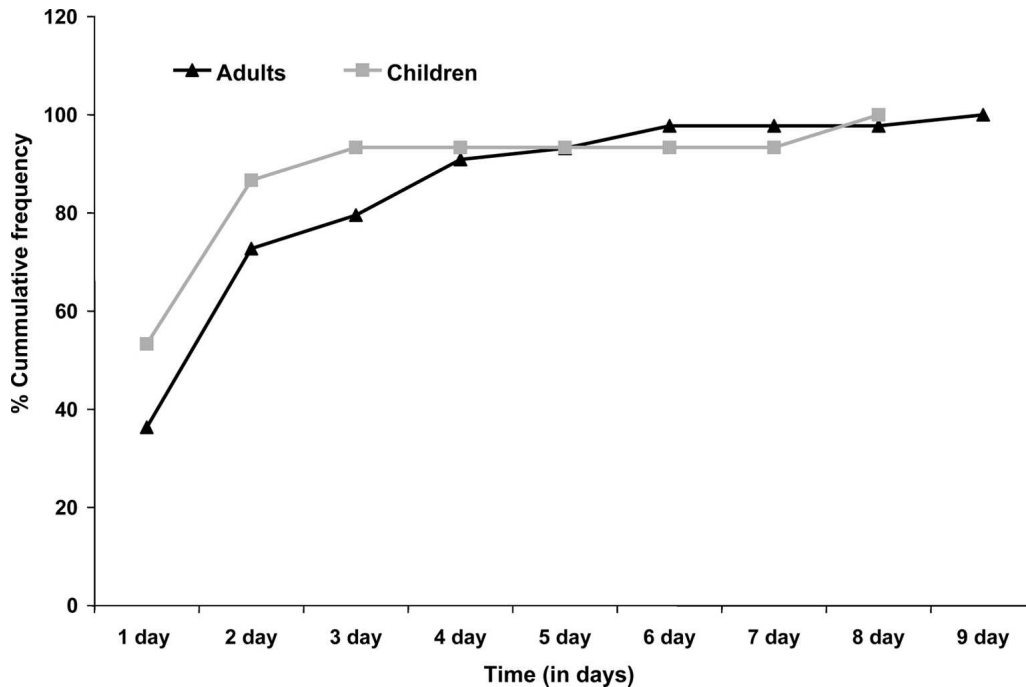


FIGURE 3. Time of recovery after admission (in days) among adults and children.

common complication among malaria cases of *P. falciparum* admitted over the study period (accounted for > 50% of all such cases). A reduction in the morbidity and mortality associated with CM may only come about by a better understanding of the disease etiology.

Fever is a characteristic feature of *P. falciparum* infection,³ yet a significant proportion of our CM patients (20%) were afebrile on admission, probably because of self-medication with anti-malarial/anti-pyretic drugs by the patient before admission.²²

In this study, seizures were observed in 25% of adults, although a previous study recorded seizures in 17% of the cases in eastern India¹³ and 60% of subjects in Bangladesh.²³ Further seizures and SMA were common in children,⁷ whereas multi-organ involvement was relatively uncommon compared with adults as recorded in other studies.^{3,7,12} Additionally, the incidence of SMA has increased with the spread of the chloroquine (CQ)-resistant *P. falciparum* parasite.²⁴ Patients may improve clinically, but unless the parasites are cleared completely, the hemoglobin level is lowered, and the patient becomes prone to life-threatening anemia.²⁵ Another serious cause of concern is the occurrence of high ARF. Many deaths were recorded in CM patients either because of ARF alone (9.75%) or in combination with other serious complications (26.82%) as recorded earlier in eastern India.¹² An increasing trend of ARF has been recorded,²⁶ which may be caused by the inappropriate use of drugs, resulting in direct nephrotoxicity, hemolysis,²⁷ or severe jaundice.²⁸ The prognosis for CM cases that develop MODS seems poor both in adults and children (41.4%) in this study as recorded in western India²⁹ (82.4%) and in eastern India¹³ (59%).

Hypoglycemia is particularly important in CM patients. We found hypoglycemia in 4% of patients. The results are in line with other studies.^{11,13} Oral quinine may also cause hypoglycemia; therefore, blood glucose level should be properly maintained throughout the course of treatment.

Neurologic sequelae in cerebral malaria have been described by several investigators from India and abroad both in adults and children.^{30–33} The occurrence of long-term neurologic sequelae was uncommon in this study as recorded in another study from Maharashtra²² and from eastern India.¹³ Newton and Krishna³ stated that neurologic sequelae were not commonly observed in non-immune adults. However, Kochar and others¹¹ recorded a 14.5% neurologic sequelae rate in survivors of CM. An increased incidence of acute and delayed cerebellar ataxia in northwest India was also observed.³²

The case fatality rate was 21% in this study. However, the mortality caused by CM varies from 8% to 33% in various countries: 8% in Zambia,³⁴ 13.9% in Thailand,³⁵ 32.7% in Bangladesh,²³ and 23–33% in India.^{11,13,14} Furthermore, in this study, a large number of patients died soon after hospitalization. More than 40% of the CM-related deaths occurred within 24 hours of admission, before the patients had complete therapy. All the Day 1 deaths (44%) were probably the result of the late referral of the patients to a tertiary care facility or because of lack of transportation from remote areas.¹⁴ Similar results have been reported by other investigators.^{13,36–40} There is clearly a need for prompt institution of therapy for any subject with multiple malaria complications presenting at primary or secondary levels of the health care system.

Thrombocytopenia was common in falciparum malaria, with spontaneous recovery on treatment. Both leukopenia⁴¹ and leukocytosis⁴² have been observed in malaria. MM infections were not associated with any of the features of CM in this study. MM cases presented with fever, headache, and vomiting. Mortality did not occur provided appropriate anti-malarial treatment was instituted timely.

In conclusion, the early effective treatment of falciparum infection is critical in preventing progression to severe, life-threatening disease. Falciparum malaria has become increasingly refractory to CQ, the most widely used anti-malarial in

India, thereby increasing the numbers of severe disease cases.⁴³ An evaluation of local problems and an appropriate epidemiologic information system are prerequisites for any control program. Early detection, prompt management, and adequate supportive therapy may improve the survival rate of CM.^{44,45}

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