Spectrum of malaria complications in an intensive care unit

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ABSTRACT

Introduction: Malaria remains a major health concern in tropical and subtropical countries. A large number of cases of malaria have been reported from the State of Orissa, India. Severe malaria cases are reported throughout the year, but they are more common during the high transmission season. The last decade has witnessed a changing pattern of presentations and complications across the country. Severe falciparum malaria is an important cause of multiple organ failure in Indian intensive care unit (ICU) patients.

Methods: All patients with severe falciparum malaria above the age of 14 years admitted to the ICU were included in this study. The clinical spectrum of severe falciparum malaria in a tertiary care level III ICU was analysed from December 1998 to June 2008. In all, there were 301 patients with severe malaria admitted to the ICU during that period.

Results: Most patients (66.9 percent) had a history of fever for less than seven days. The age distribution of the patients was 38.24 +/− 14.24 years. The Sequential Organ Failure Assessment score at admission to the ICU was 10.44 +/− 4.26. The median duration of ICU stay was three days (range 0–15 days) and 42 percent of the patients required ventilator support. Approximately 48 percent and 42 percent of patients required blood component transfusion and renal replacement therapy, respectively. The rate of single organ involvement was relatively low and multi-organ dysfunction was very common. Jaundice with acute renal failure (ARF) was the most common presentation (13.28 percent), followed by cerebral malaria with jaundice and ARF (6.37 percent), and jaundice, ARF and acute respiratory distress syndrome (ARDS) (5.31 percent). The overall mortality rate was 35.4 percent. Multivariate logistic regression analysis was conducted to estimate the association of the complications with mortality. Shock, ARF, seizure and ARDS were associated with higher mortality.

Conclusion: Severe falciparum malaria is a common cause of multi-organ failure in the ICUs in eastern India. There has been no change in the pattern of presentations over the last ten years in the east Indian state of Orissa. Apart from early diagnosis and treatment, good supportive care is the mainstay for better outcome in these cases.

Keywords: clinical spectrum, ICU, malaria complications

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INTRODUCTION

Malaria remains a major health concern in tropical and subtropical countries. Of the four *Plasmodia* species, *Plasmodium (P.) falciparum* infection is associated with different types of complications and significant mortality. Reports from the National Vector Borne Disease Control Programme (NVBDCP) have indicated that around 1.8 million cases of malaria and 1,000 malaria-related deaths occur annually in the country.[1] However, the World Health Organization (WHO) estimates that there are about 20 million cases of malaria and 15,000 deaths annually in India.[2] The intensity of transmission of malaria in India is usually low with foci of intense transmission in several states.

A large number of malaria cases have been reported from the State of Orissa, India, where this study was conducted. Orissa is situated in the eastern part of India and comprises 3.6% of India's population. However, it has contributed to 21.8% of the total cases of malaria, 39.5% of the total *P. falciparum* cases and 29.8% of deaths in the country.[1] Although severe cases of malaria are reported throughout the year, they are more common during the high transmission season, between September and December each year. Malarial complications occur in all age groups, but the frequency of complications differs depending on age. While cerebral malaria occurs in equal frequency in children and adults, severe anaemia and convulsions are more common, jaundice is less common, and acute renal failure (ARF) and acute

Table I. Proportion of deaths with different complications (n = 301).

Complication	No. of patients	No. of deaths	Proportion of death (%)
CM only	13	3	23.07
ARF only	4	-	-
Jaundice only	17	1	5.88
ARDS only	7	1	14.28
Shock only	4	1	25.00
Jaundice + ARF	40	9	22.50
CM + Jaundice	8	4	50.00
CM + ARF	5	3	60.00
CM + Jaundice + ARF	19	6	31.58
Jaundice + ARF + ARDS	16	11	68.75
Shock + other complications + ARF	42	33	70.20
Shock + other complications (without ARF)	18	9	50.00
Without any of the above complications	108	25	23.14

CM: cerebral malaria; ARF: acute renal failure; ARDS: acute respiratory distress syndrome

respiratory distress syndrome (ARDS) rarely occur in young children.[3]

The last decade has witnessed a changing pattern of presentations and complications across the country.[4] The factors responsible for an increase in the proportion of deaths have not been ascertained, although there are a large number of reports across the country indicating a shift in the clinical presentation of malaria cases from a single complication to multiple complications. A significant increase in the incidence of jaundice and ARF has been reported from several centres across the country. Severe falciparum malaria is an important cause of multiple organ failure in Indian intensive care unit (ICU) patients.[5] This paper analysed the frequency of different complications in patients admitted to an ICU situated in a malaria-endemic area so as to determine the association of individual complications with malaria-related mortality.

METHODS

The study was undertaken at Kalinga Hospital, Bhubaneswar, India, which is located in the state of Orissa in the eastern part of India. The hospital is a 250-bed private tertiary care hospital with modern facilities for patient care. It consists of a level three, 13-bed multi-disciplinary ICU that receives referred cases of severe falciparum malaria from all parts of the state for organ support and intensive care. About 35 (range 20–50) patients with severe malaria are admitted to the ICU every year, usually with multiple complications.

Severe falciparum malaria cases were usually referred to our hospital after treatment, when the complications could not be managed locally. The diagnosis of falciparum malaria was done by positive slide microscopy and/or by PfHRP2 antigen positivity. Since the majority of the cases were referred from other hospitals that had received partial treatment, and were therefore slide negative but PfHRP2 antigen positive, it was not possible to do a parasite count. All patients aged above 14 years who were admitted to the ICU with features of severe falciparum malaria, according to the WHO criteria 2000,[6] between December 1998 and June 2008, were included in the study.

Briefly, the diagnosis of severe malaria was confirmed if the patient possessed one or more of the following complications: (1) Cerebral malaria: these are malaria patients who have 'unrousable coma'. Unrousable coma is defined as a best motor response to noxious stimuli that is 'non-localising' and a best vocal response that is considered 'incomprehensible'. In the modified Glasgow Coma Scale (GCS), it usually corresponds to a score ≤ 9. If the unconsciousness has developed after a convulsion, it should persist for more than 30 minutes to exclude a postictal state. Other causes of coma, such as meningitis and encephalitis, were excluded; (2) Acute renal failure: this includes a urine output < 400 ml in 24 hours with plasma creatinine > 3.0 mg/dl; (3) Jaundice: this is a yellow colouration of sclera with plasma bilirubin > 3.0 mg/dl; (4) Pulmonary oedema/ARDS/acute lung injury: this indicates the presence of tachypnoea, dyspnoea and basal crepitations. The ratio of PaO_2/ FiO_2 is ≤ 300; (5) Severe anaemia: this occurs when the blood haemoglobin is < 5.0 gm/dl, or when the haematocrit is < 20% plus 100,000 parasites/Ul; (6) Hypoglycaemia: the plasma glucose is < 40 mg/dl; (7) Severe acidosis: the plasma venous bicarbonate is < 15 mmol/l or the pH is < 7.1; (8) Peripheral circulatory failure: systolic blood pressure is < 80 mm Hg with cool peripheries.

The inclusion criteria included all patients with severe falciparum malaria who were above the age of 14 years and admitted to the ICU. In all, 301 cases were analysed. All patients with severe falciparum malaria

Table II. Complications due to falciparum malaria in ICU and their association with mortality.

No.	Complication	Proportion (%)	Odds ratio (95% CI)
1	Jaundice (serum bilirubin > 3 mg%)	73.3	1.30 (0.7–2.5)
2	Acute renal failure (serum creatinine > 3 mg%)	61.8	3.47 (1.9–6.5)
3	Glasgow Coma Scale score < 7	35.4	0.71 (0.4–1.3)
4	Acute respiratory distress syndrome	31.5	2.16 (1.2–3.9)
5	Shock (systolic BP < 90 mm Hg)	25.3	4.35 (2.4–8.0)
6	Seizure (single or multiple episode)	21.8	2.50 (1.51–4.1)
7	Secondary infections	19.7	1.06 (0.5–2.1)
8	Metabolic acidosis	15.8	-
9	Severe anaemia (Hb < 7 gm% or PCV 20%)	2.7	-
10	Disseminated intravascular coagulation	2.0	-
11	Hypoglycaemia (blood glucose < 40 mg%)	1.4	-

CI: confidence interval; BP: blood pressure; Hb: haemoglobin; PCV: packed cell volume

Table III. Complication rates in first five years (1999–2003) and the next five years (2004–2008).

Complication	No. of patients (n = 301)	
	1999–2003	2004–2008
CM only	6	7
ARF only	2	2
Jaundice only	12	5
ARDS only	4	4
Shock only	-	4
Jaundice + ARF	20	20
CM + Jaundice	3	5
CM + ARF	3	2
CM + Jaundice + ARF	11	8
Jaundice + ARF + ARDS	6	10
Shock + others + ARF	19	23
Shock + others + without ARF	9	9
Without any of the above complications	54	54

CM: cerebral malaria; ARF: acute renal failure; ARDS: acute respiratory distress syndrome

aged ≤ 14 years were excluded from the study. This was primarily an adult ICU with very few paediatric admissions. Ten patients who were < 14 years of age were excluded.

Patients were moved from the ICU to the High Dependency unit located inside the ICU complex, or shifted to the ward directly, once they were fit enough to be managed in those locations. They were followed up in the wards until discharge.

The history and clinical features were prospectively recorded in a pre-designed form in all cases. Sequential Organ Failure Assessment (SOFA) and GCS scores were taken at admission. Thick and thin blood films were examined for malaria parasite, and the PfHRP2 antigen rapid diagnostic test was conducted in all cases. Blood sugar was estimated eight-hourly using a glucometer. Complete blood count, serum urea and creatinine, serum electrolytes, liver function test and ECG were evaluated in all cases on admission and at appropriate intervals. Chest radiograph and arterial blood gases were done when necessary. All investigations conducted on admission and during the hospital stay were entered into the form.

All patients were treated using quinine or artesunate and given supportive therapy, such as airway management, fluids, electrolytes, haemodialysis, ventilation, vasopressors, blood products and antiepileptics, when indicated.

RESULTS

Most patients (66.9%) had a history of fever for less than seven days. The age distribution of the patients was 38.24 ± 14.24 years. The SOFA score at admission to the ICU was 10.44 ± 4.26. The median duration of ICU stay was three days (range 0–15 days), and 42% of the patients required ventilator support. Approximately 48% and 42% of the patients required blood component transfusion and renal replacement therapy, respectively. There was a 35.4% mortality rate among these patients in the ICU.

The most common presentation was jaundice with ARF, followed by cerebral malaria along with jaundice

and ARF, and jaundice along with ARF and ARDS. The mortality increased as the number of complications increased. Table I shows the major complications observed in these patients. In the majority of patients with jaundice, there was conjugated hyperbilirubinaemia with a variable elevation of the hepatic enzymes (serum glutamic oxaloacetic transaminase: median 118, range 10–1066; serum glutamic pyruvic transaminase: median 60.7, range 17–795). Multivariate logistic regression analysis was conducted to estimate the association of the complications with mortality, taking survival as the dependent variable. The complications that were observed in nearly 2% or more of the patients (shock, ARF, seizure and ARDS) were the factors associated with higher mortality (Table II).

We also explored whether there has been a changing pattern of complications encountered in our ICU among falciparum malaria patients. The complication rates in the first five years (1999–2003) were compared with those of the next five years (2004–2008). The complication rates in both time frames were comparable (Table III).

DISCUSSION

Mortality due to severe falciparum malaria was found to be 35.4% in this study. In a similar study in the western part of India by Krishnan et al, the mortality was 48.8%.[5] According to large-scale studies performed in endemic areas, mortality among adults with severe malaria treated by highly trained teams ranged from 10% to 25%.[6] The incidence of jaundice and renal failure in our series was higher and that of cerebral malaria was lower compared to Krishnan et al's series.[5] Kochar et al reported a changing pattern in the presentations of falciparum malaria from the northwestern part of India. They stated that the important cause of mortality in 1994 was cerebral malaria, whereas multiple organ dysfunction syndrome, with a predominant presentation of jaundice and renal failure, was the main cause in 2001.[4] Our data from 1998 to 2008 showed a predominance of jaundice and renal failure, similar to Kochar et al's data from 2001.[4] Four WHO major criteria that were present within 24 hours of admission were strongly correlated with in-ICU mortality, namely, unrousable coma, pulmonary oedema, shock and metabolic acidosis, even after adjustment for multiple comparisons.[7] In our study, shock, ARF, seizure and ARDS were associated with higher mortality (Table II).

In conclusion, severe falciparum malaria is a common cause of multi-organ failure in the ICUs in eastern India. There has been no change in the pattern of presentations over the last ten years in Orissa in the eastern part of India. Apart from early diagnosis and early treatment, good supportive care is the mainstay for better outcomes in these cases. Shock, ARF, seizure and ARDS were factors associated with higher mortality.

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