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Prediction of outcome of severe falciparum malaria in Kolhapurin western India: A hospital-based study

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ABSTRACT

Background and Objectives:
A hospital-based study was conducted to elucidate the different severe clinical presentations of falciparum malaria and to examine the critical clinical and laboratory parameters on the prognosis of these severe manifestations
Materials and Methods:
Continuous and normal distributed data were compared by two-tailed Student's t-test and proportions compared with$\chi 2$ tests with Yates' correction or Fisher's exact test.
Results and Discussion:
A total of 1320 patients with clinical malaria, diagnosed at outpatients' department were admitted in the hospital during the 1 year study period of which, 292 (22.1%) were children under 14 years of age. The major clinical categories on admission were hyperpyrexia (70.7%), cerebral malaria (9.4%), malarial anemia (7.7%), algid malaria (1.5%), and malaria associated categories were respiratory infection (2.2%), hepatitis (2.0%), urinary tract infection (1.8%), enteric fever (3.3%), and sickle cell disease (1.2%).

KEYWORDS | Falciparum malaria, severity, prediction, outcome

INTRODUCTION

Approximately 3.3 billion people, living in 99 countries are at risk of malaria, of which, 207 million develop symptomatic malaria annually.[1] Majority of these are caused by infection with Plasmodium falciparum with an average of 650,000 deaths each year between 1980 and 2010.[2] About 60% of the clinical episodes and 86% of the 627,000 deaths in 2012 occurred in children <5 years in Africa, south of the Sahara, where malaria accounts for 25-35% of all out-patient visits, 20-45% of hospital admissions and 15-35% of hospital deaths.[1,2] India reported 1.3 million malaria cases of which 0.6 million P. falciparum cases and 754 deaths in 2011.[3] Therefore, there is a need for more site-specific data in order to appreciate the complete clinical and epidemiological picture for efficient testing of candidate malaria vaccines and other control tools in future in different endemic sites.[13] This study highlights the different categories of severe malaria, seasonal pattern of hospital admission of malaria cases, clinical management practices and the outcome in a major referral hospital situated in a tribal area endemic for falciparum malaria in maharashtra state of India.

MATERIALS AND METHODS

Study setting

The study was carried out in the District Headquarters Hospital (DHH), Koraput in Odisha State, India. Transmission of malaria is perennial with two peaks: First in rainy (July–August) when the vector, Anophelesculicifacies breed in rice fields and second in winter season (December–January) when the vector, Anopheles fluviatilis breeding in streams plays a role.[14] Malaria infection is mostly due to P. falciparum (80-90%) and the major vector is A. fluviatilis.[15] Chloroquine (CQ) was the first line treatment for P. falciparum until 2009. It was replaced with artemisinin combination therapy (artesunate, sulfadoxine + pyrimethamine) from 2010 due to the development of P. falciparum resistance to CQ.[16]

Study design and participants

Consecutive patients, admitted at the DHH with the clinical diagnosis suggestive of acute malaria, from April 2011 to March 2012 were screened for severe malaria following WHO criteria.[17,18] Physicians documented findings of clinical examination, including vital signs twice daily during the course of illness from the time of admission to the time of discharge from the hospital.

The criteria of severity were followed as per WHO guidelines[17] along with slide parasite positive were taken for the study and detailed analysis. Only those fulfilling the criteria were retained in the study. The respiratory distress due to malaria was diagnosed based on exclusion of other causes of respiratory distress and positive response to antimalarial treatment. Sickling test was done following the method Dacie and Lewis.[19]

Data and statistical analysis

All study data were captured on a structured case report form bearing patient demographic and identification numbers. All clinical data were reviewed before being double entered into a computer. Statistical analyses were carried out with Epi Info, version 6, statistics program for public health, center for Disease Control and Prevention, Atlanta, Georgia, USA, 1996). Continuous and normal distributed data were compared by two-tailed Student's t-test and proportions compared with $\chi 2$ tests with Yates' correction or Fisher's exact test. Basic statistics were calculated for the baseline characteristics: Gender, age group, weight, fever, presenting symptoms, point estimates using proportions and means, and 95% confidence intervals were computed for the clinical and laboratory features. Significant differences were tested using confidence intervals of the difference or odds ratio and the corresponding (95%) confidence intervals and P values. A $P< 0.05$ was considered as statistically significant.

RESULTS

Clinical categories with symptoms of malaria patients on admission

A total of 1320 patients with clinical malaria were admitted in the hospital during the 1 year study period of which, 292 (22.1%) were children under 14 years of age. Highest number of cases (200) was admitted in the month of July **[Figure 1]**. The average days of fever, headache, vomiting, and chill/rigor on admission were 5.7 (+4.1), 5.1 (+3.8), 3.8 (+4.4), and

6.5 (+5.5) respectively in adults and 4.9 (+3.9), 4.8 (+2.0), 3.1 (+2.1), and 5.2 (+2.8) in children. The major clinical categories were hyperpyrexia (70.7%), cerebral malaria (9.4%), malarial anemia (7.7%), algid malaria (1.5%), and malaria associated categories were respiratory infection (2.2%), hepatitis (2.0%), urinary tract infection (1.8%), enteric fever (3.3%), and sickle cell disease (1.2%). The proportion of children and adults admitted in each clinical category is given in **Table 1.**

(fig 1 comes here)

Month-wise number of malaria patients admitted in the district hospital, Kolhapur

(TABLE 1 COMES HERE)

Categories of confirmed severe malaria in children and adults in admitted malaria patients

Hyperpyrexia in children and adults

Hyperpyrexia was the predominant clinical manifestation both in children and adults. The mean hemoglobin (Hb) concentration, total leucocyte count, blood urea, and serum creatinine, and random blood sugar levels were within normal range, whereas serum bilirubin was above the normal values in adults. The mean values of Hb concentration (8.7 g/dL) and serum bilirubin (0.2 mg/dL) were below the normal values in children with hyperpyrexia

[Table 2 COMES HERE)].

Malarial anemia in children

In all, 14 children (13.0%) below 14 years of age had malarial anemia. The mean Hb level was 7.8 g%. About 19% of children with anemia had Hb concentration of <7 g% requiring blood transfusion. Children with malarial anemia had severe anemia when associated with sickle cell disease. Children with severe anemia had more respiratory distress than those without [Table 3].

(TABLE 3 COMES HERE)

Causes of deaths in malaria patients admitted in the district hospital, Kolhapur

Duration of hospital stay

The duration of hospital stay varied between 2 and 10 days, the lowest being in cases of malaria with urinary tract infection and highest in cases of malaria with respiratory tract infection [Figure 2].

(Figure 2 **COMES HERE)**

Average number of days of hospital stay of different severe malaria cases admitted in the district hospital, Kolhapur

Seasonal variation

Of the 1320 cases of severe malaria enrolled during the 1 year study period (April 2012 to March 2013), 47.6% were enrolled in June-September (rainy season), 31.4% in February-May (summer season), and 21% in October-January (winter season) [Figure 1].

Factors associated with malaria death

The overall case fatality rate (CFR) (adult and child combined) was 4.3 (57/1320) during the 1 year study period. The ratio was similar in male and female. The major cause of death was cerebral malaria (45.6%). This could be due to late arrival of patients to the hospital from rural areas. The second most important cause of death was malaria along with respiratory infection (19.3%) and anemia (10.5%). However, malarial anemia along with sickle cell disease accounted for 19.3% of all malaria related deaths [Table 3]. The CFR in children (12.3) (36/292) was significantly higher (P< 0.05) than adults (2.0) (21/1028). The proportions of deaths due to malaria associated respiratory infection and sickle cell disease in children were significantly higher when compared to adults. However, proportion of mortality due to acute renal failure was higher in adults. Though cerebral malaria and malaria related respiratory infection were the leading cause of mortality in children, the effect of malaria related anemia and sickle cell disease also played a major role in poor prognosis in children. Therefore, children with severe anemia (<7 g/dL) due to cause cited above could not be saved in spite of a blood transfusion.

DISCUSSION

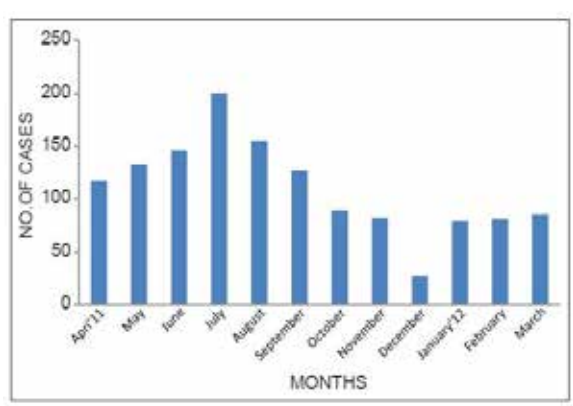
The present study area with overall malaria CFR of 4.3 and child CFR of 12.3 and no significant difference between the genders could be a suitable site for drug and vaccine efficacy trials. This study indicates that cerebral malaria and severe anemia are the major causes of mortality. These two independent clinical entities confirms the fact that severe anemia due to chronic blood loss and cerebral involvement are the factors that are most associated with poor outcome. Sickle cell disease also resulting in anemia could be an added factor in precipitation of poor prognosis of severe anemia cases. The observation that six cases (four children and two adults with severe anemia with Hb concentration <7 g/dL) could not be saved in spite of blood transfusion suggest that it can be important indicator especially in children to evaluate malaria control program because of its frequency, especially in children and ease with which it can be measured with certainty in field situations. Respiratory infection, though the most frequent associated clinical feature, was a poor predictor of death independently, perhaps because most of cases might have received some form of antibiotic therapy before admission at the hospital. Acute renal failure, probably as a result of electrolyte imbalance due to severe dehydration prior to hospitalization has poor prognosis in cases of adult patients. Increase in serum bilirubin in cases of hyperpyrexia, cerebral malaria, and malaria associated with respiratory infection both in adult and children patients suggest derangement of liver function. Increase in blood urea, serum creatinine, serum bilirubin, and random blood sugar level in cerebral malaria cases both in children and adults indicate involvement of multiple organs. The clinical and laboratory manifestations were also consistent with reports in other endemic settings. This study represents only hospital admitted cases instead of community data suggesting that this finding may be an underestimation, as some cases might have died at home during the period since almost all cases of untreated severe and complicated malaria are potentially fatal.

CONCLUSION

Severe forms of malaria in the study area occur frequently, the predominant feature being cerebral malaria and severe anemia. Though perennial, most of the severe malaria occurs during monsoon, high transmission season. The findings suggest that the area could be effectively managed by sustained and continuous preventive and curative efforts. Clinical signs suggest multi organ dysfunction (e.g. renal failure, pulmonary edema leading to respiratory distress syndrome, hepatic damage). Acute renal failure in adults and severe anemia with Hb concentration <7 g/dL and cerebral malaria had poor prognosis.

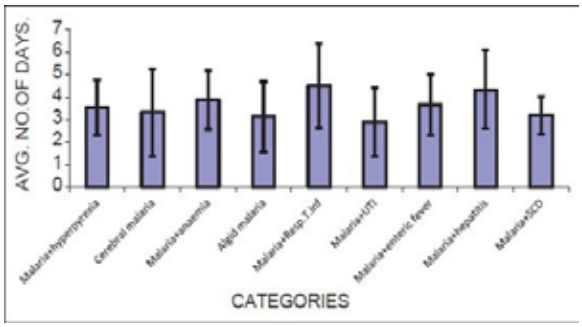
Tables and figures:

Figure 1



Month-wise number of malaria patients admitted in the district hospital, Kolhapur

Figure 2



Average number of days of hospital stay of different severe malaria cases admitted in the district hospital, Kolhapur.

Table 1:Categories of confirmed severe malaria in children and adults in admitted malaria patients

Complications	Adults (>14 years) N=533 (%)	Children (<14 years) N=108 (%)	*P* value
Hyperpyrexia	373 (70.0)	46 (42.6)	<0.05*
Cerebral malaria	53 (9.9)	20 (18.5)	<0.05*
Malarial anemia	21 (3.9)	14 (13.0)	<0.05*
Respiratory infection	18 (3.4)	11 (10.2)	<0.05*
Sickle cell disease	7 (1.3)	5 (4.6)	>0.05
Algid malaria	16 (3.0)	5 (4.6)	>0.05
UTI	17 (3.2)	4 (3.7)	>0.05
Enteric fever	17 (3.2)	2 (1.8)	>0.05
Hepatitis	11 (2.1)	1 (1.0)	>0.05

*Statistically significant. UTI: Urinary tract infection

Table 2: Biochemical parameters in major clinical categories of severe malaria cases in adults and children

Parameters	Hyperpyrexia		Cerebral malaria		Malarial anemia		Respiratory infection	
	Adults	Children	Adults	Children	Adults	Children	Adults	Children
Haemoglobin (g/dL)	10.35 (7.4-14.4)	8.72 (4.4-13.0)	9.6 (7.4-12)	8.92 (5.6-11.4)	8.7 (7.4-15)	7.07 (3.5-11)	10.6 (8-13)	9 (5-11)
Bilirubin (mg/dL)	3.77 (0.5-16.6)	0.7	4.6 (2.4)	1.8 (0.6-3.0)	3.4 (2.1-14.7)	1.85 (0.7-3.2)	3.06 (1.56-5.9)	NA
TLC (/µl)	8775 (4200-12,000)	8954 (4800-12,300)	8880 (7600-10,700)	9592 (8200-11,900)	8967 (6900-12,900)	7266 (2900-9950)	7808 (7716-10,300)	9612 (7900-10,900)
Urea (mg/dL)	39.48 (8-156)	26	43.25 (19-220)	NA	36.03 (18-100)	NA	32.8 (20-51)	NA
Creatinine (mg/dL)	1.3 (0.2-12.0)	0.6	2.14 (0.7-9.4)	1.6	1.07 (0.3-2.0)	NA	0.77 (0.4-1.5)	NA
RBS (mg/dL)	170 (41-499)	108	175 (65-557)	179	99.3 (45-166)	135	118 (88-163)	178

Normal values - Creatinine: 0.7-1.2 mg/dL, Random blood sugar: 70-140 mg/dL, Urea: 15-40 mg/dL, Bilirubin: 0.4-1.2 mg/dL, RBS: Random blood sugar, TLC: Total leucocyte count: 4000-10,000/ µl, NA: Not available

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