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Clinical presentation and Predictors of mortality in severe malaria in pediatric population: A prospective observational study

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Abstract
Background: Malaria remains a significant public health in India and a major cause of under 5 mortality. Clinical manifestations of malaria in children may differ significantly from adults and there is wide variation in manifestation depending on endemicity. We conducted this study to find the clinical presentation and features which would predict mortality in children with severe malaria.
Methods: a prospective observational study was conducted at Pediatric units of SCB Medical College, Cuttack. Children below 14 years of age with confirmed diagnosis of malaria and satisfying the WHO criteria for severe malaria were included in the study. Baseline demographic data collected and clinical features during the course of illness were documented. Logistic regression analysis was used to find the predicting factors for mortality.
Result: out of 557 cases with malaria over a period of 20 months, 130 patients (23.3%) satisfied the WHO criteria for severe malaria. Case fatality rate was 8.5%. Apart from fever, anemia and prostration were most commonly associated complications. Presence of respiratory distress, CNS involvement, shock and renal failure were found to be the major predictor of death. Risk of mortality increased significantly with the presence of multiple organ dysfunction. About 12.3% of the patients were G6PD deficient. A higher incidence of hemoglobinuria and a lower incidence of cerebral malaria was observed in G6PD deficient patients.
Conclusion: Complications associated with severe malaria in pediatric populations in India differ from African countries. Multiple organ dysfunction is not uncommon in the pediatric population and it significantly increases the chances of adverse outcome.

Keywords: Malaria, mortality, G6PD, hemoglobinuria, cerebral malaria

Introduction
Malaria continues to be a major global health problem [1, 2]. More than 40% of the world's population are at risk for malaria to varying degrees in countries with on-going transmission [1]. In African countries, it accounts for about 20% of mortality in children under five of age [3]. Severe malaria generally has a poor prognosis with a 10–30% case fatality rate [4, 5, 6]. African countries account for the majority of malaria related childhood deaths worldwide. Malaria is a public health problem in several parts of India. About 95% population in the country resides in malaria endemic areas and 80% of malaria reported in the country is confined to areas consisting 20% of the population residing on tribal, hilly, difficult and inaccessible areas [7, 8]. The number of cases of malaria and death due to malaria in India has decreased substantially in last 25 years after implementation of national programs to control malaria [8]. A wide spectrum of clinical manifestations has been described in literature. Most of the clinical descriptions of malaria are from data obtained from sub Sharan Africa. There are very few studies which have described the spectrum of presentation of malaria in pediatric population from the Indian subcontinent. Malaria contributes significantly to under 5 mortality and there are only few studies from the region have described the predictors of mortality in severe cases of malaria. The current study was conducted at a tertiary level hospital from eastern India, a high endemic area for malaria transmission, to find out the clinical features which significantly predict mortality in this group of pediatric patients.

Materials and Methods

The present study was a prospective cohort study conducted in the departments of pediatrics at SCB Medical College, Cuttack, which serves as the largest referral center for sick children in Orissa. The period of the study was from January 2011 to August 2012.

Study Population

Febrile children below 14 years of age admitted to the Pediatric unit with the laboratory diagnosis of malaria were included in the study. Children with fever who were found to have a negative laboratory test for malaria were excluded from the study.

Recruitment

All children with fever as a clinical presentation at time of admission were assessed for eligibility. Patients who were found positive for malaria by microscopic examination of thick blood smear or indirect methods like immunochromatography or quantitative Buffy coat examination were included and Patients with alternate explanations for fever were excluded from the study. Written informed consent was obtained from the parents prior to enrollment. Demographic and clinical data were obtained in a prechecked, validated pro forma. Clinical features including various complications, laboratory investigations were documented. For confirmation of cases, microscopic examination of blood or other rapid diagnostic tests (immunochromatography, Quantitative Buffy coat examination) was done.

Both thick and thin smear were prepared and examined under light microscope. To prepare blood smear, 3rd or 4th finger of the left hand was wiped with alcohol, allowed to dry and subsequently pricked at the distal part of the Palmar aspect under all aseptic conditions. For preparing a thick smear, a large drop of blood is taken in the center of the slide. With the help of a needle or the corner of a slide the drop is spread over ½ x ½ inch area. When dry the thickness should be such that the printed matter can just be read through it. For thin smear, one drop of blood not larger than a pin head was taken on grease free clear slide at a distance of about half an inch from right end. The smooth edge of another glass slide held at an angle of 45° in contact with drop of blood, then lowered to angle of 30° and then gently pushed to the left, till the blood is exhausted. The smear is subsequently allowed to dry. The smear was stained with giemsa stain and examined under light microscope.

Glucose 6 phosphate dehydrogenase enzyme activity was estimated in all cases of malaria. Quantitative estimation of enzyme activity was done from peripheral blood. Quantitative measurement of G6PD enzyme was done by using commercially available kit which involved measurement of the rate of increase in reduction of NADP to NADPH and its spectrophotometric absorbance at 340 nm. G6PD enzyme activity less than 4.6 U/gm was considered as deficiency. The end point of the study was death or discharge from the hospital. The outcomes of the study were to find the complications associated with malaria and compare complications and clinical outcomes between groups with normal and reduced G6PD activities.

Statistical analysis

Collected data were entered into an electronic database created in the Microsoft® office excel® 2007 (Microsoft, Redmond, CA, USA) Microsoft, Redmond, CA, USA. Baseline variables were documented using descriptive statistics. Mean and standard deviation was calculated for continuous data. Incidence of associated complications was calculated as percentage of total cases. To find the strength of association between a particular complication with mortality, odds ratio with 95% Confidence interval was calculated. Student t test was used to compare the mean between the groups. Chi square test was used to find the difference in proportion of incidence of particular complications between the two groups. A p value less than 0.05 was considered as significant. All statistical analysis was performed by using SPSS software version 10.0.

Result

A total of 557 patients was diagnosed to have malaria during the study period, out of which 130 (23.3%) patients satisfied the World Health Organization (WHO) criteria for severe malaria (2000). The Mean and median age of presentation was 7.52 years (± 3.42 years) and 7 years respectively with male: female ratio of 2.1. The majority (44.6%) of the children belonged to age group of 5 to 10 years. Only 2 cases were documented in infancy and both survived. Eleven deaths were recorded over the study period with an overall mortality rate of 8.64%. Sixteen children (12.3%) were found to be G6PD deficient and no mortality was documented in this group (Table 1).

Table 1: Age, sex and distribution of G6PD deficiency of the study cohort

Age group (in years)	No. of case (%)	Male	Female	G6PD deficient	Death
Age < 1 year	2 (1.54%)	1 (0.77%)	1 (0.77%)	2 (1.54%)	0 (0%)
1-5 year	29 (22.3%)	20 (15.4%)	9 (6.9%)	2 (1.54%)	3 (2.3%)
5-10 year	58 (44.6%)	39 (30%)	19 (14.6%)	5 (3.85%)	4 (3.07%)
>10 year	41 (31.53%)	28 (21.5%)	13 (10%)	6 (4.61%)	4 (3.07%)
Total	130	88 (67.7%)	42 (32.3%)	16 (12.3%)	11 (8.46%)

Fever was the most common clinical feature in the cohort. Apart from fever, anemia was the most common associated clinical feature, which was found in nearly 80% of patients. Severe anemia was observed in 16.1% of cases. The next common complications included prostration (50.7%), presence of encephalopathy (33.1%), clinical jaundice (23%) and oliguria (16%). Nearly 16.1% of the cohort had features of shock during the course of illness. Other clinical features like respiratory distress and clinical bleeding were documented in 9.3% and 6.9% of children respectively (Table 2). Anemia (hemoglobin < 10 g/dl) was also the most common laboratory parameter found to be altered. Leucocytosis (Total leukocyte count>15000/cmm) was found in 28% of cases out of which a bacterial pathogen could be isolated from blood culture in 13% of cases. Nearly one third of the cohort were found to have thrombocytopenia (Platelet count < 1.5 lakh/cmm), but severe thrombocytopenia (Platelet count < 50000/cm) was found only in 2.3% of cases (Table 3).

Table 2: Distribution of clinical features among the study cohort

Clinical features	Number	Percentage
Fever	130	100
Prostration	66	50.7
Anemia	104	80
Jaundice	30	23.07
Encephalopathy	43	33.07
Seizure	37	28.46
Respiratory distress	12	9.23
Oliguria	22	16.92
Hemoglobinuria	21	16.15
Bleeding	9	6.92
Edema	26	20
Hepatomegaly	90	69.23
Splenomegaly	110	84.61
Shock	21	16.15

Table 3: Laboratory parameters among the study cohort

Laboratory parameter	Number	Percentage
Anemia (Hb < 10 g/dl)	104	80
Severe anemia (Hb < 5 g/dl)	21	16.15
Leucocytosis (TLC > 15000)	37	28.46
Leucopenia (TLC < 4000)	2	1.53
Thrombocytopenia (<150000)	41	31.53
Severe thrombocytopenia(Platelet < 50000)	3	2.3
Serum creatinine > 3 mg/dl	24	18.64
Serum bilirubin > 3 mg/dl	32	24.61
Serum bilirubin > 10 mg/dl	2	1.53
Hypoglycaemia (plasma sugar < 45 mg/dl)	12	9.23
Positive blood culture	17	13.07

Although nearly two third of the patients were male, male sex alone was not significantly associated with risk of mortality. Only one fourth of patients among the cohort were under 5 years of age. Younger age of patient did not increase the risk of mortality. Severe anemia, although a common presentation, did not predict the risk of mortality. About one in every sixth patient with features of encephalopathy died. The risk of mortality was 50%, 37.5%, and 31.6% with respiratory distress, renal failure and shock as clinical presentation. On univariate analysis, presence of respiratory distress, encephalopathy, renal failure and shock were found to be strong predictors of mortality in patients with severe malaria (Table 4).

Table 4: Prevalence of Major Clinical Criteria of Malaria and Associated Mortality

Clinical criteria	Prevalence (n=130)	Death	OR	95% CI	P value
Male sex	88	8(9.09%)	1.27	0.32-5.04	0.73
Age < 5 year	31	3(9.67%)	1.19	0.29-4.79	0.79
Severe anemia	26	1(3.84%)	0.40	0.04-3.26	0.39
Respiratory distress	12	6(50%)	11.8	3.13-44.48	0.003
Encephalopathy	48	8(16.7%)	4.55	1.15-17.99	0.03
Hepatopathy	32	5(15.6%)	2.55	0.73-8.92	0.14
Shock	19	6(31.6%)	7.01	1.94-25.28	0.003
Renal failure	24	9(37.5%)	19.8	4.03-97.94	0.002

There were 33 patients who developed features of multiorgan dysfunction with 8 patients developing clinical features involving 3 organs and 4 patients had involvement of 4 organs. About 40 % (n=52) of patients had a single organ involvement. Rest 45 (34.6%) patients did not qualify for any organ involvement as per WHO criteria. The incidence of mortality was 27.3% in the MODS group as compared to 3.8% with single organ involvement. Presence of multiorgan dysfunction significantly increased the risk of mortality among the cohort (Table 5).

Table 5: Organ involvement and associated mortality

Organ involvement	Prevalence (n=130)	Death	OR	95% CI	P value
Single organ involvement	52	2	4.33	0.20-92.62	0.34
Multiple organ involvement	33	9	25.80	1.45-459.09	0.02

Table 6: Comparison of various outcomes between normal and G6PD deficient patients

Clinical manifestation	Normal G6PD (n=114)	G6PD Deficient (n=16)	P value
Severe anemia	22(19.2%)	4(25%)	0.56
Thrombocytopenia	16(14.03%)	1(6.25%)	0.39
Encephalopathy	47(41.23%)	1(6.25%)	0.006
Hepatopathy	27(23.68%)	5(31.25%)	0.51
Renal failure	22(19.3%)	2(12.5%)	0.51
Respiratory distress	12(10.5%)	0(0%)	0.17
hemoglobinuria	9(7.9%)	7(43.75%)	< 0.001
Death	11(9.64%)	0(0%)	0.19

The prevalence of G6PD deficiency was 12.3% (and=16) in the cohort. All patients with G6PD deficiency survived. A significant number of patients (43.75%) with G6PD deficiency developed hemoglobinuria during the clinical course. Nearly one fourth of the children had severe anemia and nearly one third of patients developed features of hepatic failure. The incidence of central nervous system and renal involvement was 6.25% and 12.5% respectively. As compared to patients with normal G6PD status, patients with G6PD deficiency were found to have a significantly higher risk of developing hemoglobinuria and a statistically significant lower risk of CNS involvement (Table 6).

Discussion

The mean age of presentation of the was 7.5 years in the present study. Various studies have reported the typical age of presentation of severe malaria to be inversely proportional to endemicity [10, 11]. An earlier age of presentation is observed in many countries of Africa with high transmission rates as compared to areas with low transmission rates. In contrast to the mean age of 26 months, with 86% of the population being under 4 years of age in high-transmission areas in Africa [4]. In lower-transmission areas of Africa, such as Senegal, the mean age of presentation was around 6.2 years [6]. The mortality rate in the current study was around 8.5%. The mortality rate among all age groups were comparable. There were only 2 infants in the group who presented with severe malaria and both survived. There was no difference in mortality between males and females. This difference can be explained by the degree of endemicity, age at first infection, reinfection and immune response of the population. The prevalence of G6PD deficiency was 12.3% in the present study. Although the exact prevalence of G6PD deficiency in India is not known, various studies have reported its prevalence ranging from 2% to 27.9% in different communities [12, 13]. A recent meta analysis of 72 studies has reported the prevalence of G6PD deficiency to be around 8.5% in India [14].

A variety of clinical presentation has been described in

patients with severe malaria and the relative proportion of various complications varies across different geographic regions. More than 50% of the patients in the current study had prostration. The incidence of coma/convulsion/encephalopathy was around 33%. Similar incidences of various complications have been described by a recent study from Africa [15]. Seidlein *et al*. have reported the incidences of convulsion (31%), Prostration (54.8%), jaundice (2.1%), Respiratory distress (16%) in their study [15]. About 16% of the patients had severe anemia in the present study. Another study from the same centre have reported the incidence of anemia to be around 28% [16], but the incidence of severe anemia has not been described separately. Marsh *et al*. reported 27.5% of the African population to have severe anemia [17]. Other smaller studies from Orissa have described a similar, albeit slightly lower, the prevalence of anemia in pediatric patients [18, 19, 20].

Presence of G6PD deficiency may protect from severe form of malaria. The proective role of G6PD deficiency has been described by few studies from Africa and South East Asia [21, 22, 23]. This might provide a survival advantage in malaria endemic area. Malaria parasite commonly thrives in mature red cells. As hemolysis affects mature red cells more readily, there are fewer of them to host malaria parasites. Hemolysis of mature red cells in G6PD deficient individuals might explain the degree of protection against severe forms of malaria in such individuals [25]. Luzzatto *et al*. studied the infection rate of parasites in normal and deficient red cells *in vitro* and found that the malarial parasite selectively infects the cells that are normal for G6PD [26, 27]. In another study it has been shown that the malarial parasite has its own G6PD gene, which is turned on selectively [28]. However, in the case of heterozygotes the parasite encounters both normal and deficient cells and is therefore not able to turn on its own gene and is thus at a survival disadvantage [28]. In contrary, patients with G6PD deficiency experience intravascular hemolysis following exposure to antimalarial agents. Primaquine, a drug used in combination therapy with artemisinin derivatives is well known to cause intravascular hemolysis in such individuals [29]. Besides primaquine, quinine and artemisinin compounds has also been shown to cause hemolysis in G6PD deficient individuals [30, 34]. In the present study, we compared the rate of complications among individuals with normal and deficient G6PD level. The rate of various complications was comparable between the two groups except a significantly high incidence of hemoglobinuria and a relatively lower incidence of cerebral malaria in individuals with G6PD deficiency.

The mortality rate in the present study was 8.5%. The presence of various complications, multiple organ involvement increases the risk of mortality. We found that presence of respiratory distress, Central nervous system involvement, shock and renal failure in the course of disease significantly predict the risk of mortality. Again the presence of multiple organ dysfunction (MODS) also significantly increases the probability of death. There was no significant effect of age in predicting death as an independent variable. Mortality was not significantly different in under 5 years of age. Though severe anemia was a common complication in the course of disease, it also did not predict death as an independent variable. In African children from a high-endemicity area, impaired consciousness, jaundice, RD, and hypoglycemia are important predictors of death [17]. In a study from Ghana, severe anemia was present in 55% of the total cases but it did not predict the risk of mortality [35]. Tripathy *et al*. described 4 major predictors of mortality; RD, cerebral malaria, MODs, and hyperparasitemia, in their study [16]. Diagnosis of malaria was based on rapid diagnostic tests in the majority of cases (63%) in the present study. As only in 37% (n=48) cases, diagnosis was confirmed by microscopic test, we could not evaluate hyperprasitemia as a predictor. Only 6 (4.6%) patients have documented hypoglycemia during the course. Almost two third (66.7%) of patients with respiratory distress had metabolic acidosis. The WHO-South East-Asia Regional Office regional guidelines continue to list severe anemia, convulsions, hypoglycemia, and metabolic acidosis to be the most common manifestations in the pediatric population and cerebral malaria to be common in older children [36]. Multisystem involvement is described only in adults [36]. The 2006 treatment guidelines of the WHO list cerebral malaria, metabolic acidosis, severe anemia, and hypoglycemia to be the key common features and renal failure and acute pulmonary edema in adults [29].

There are few limitations in the present study. We could include only 130 cases with severe malaria in the study. Diagnosis was confirmed by rapid diagnostic tests in the majority of cases. As the number patients with G6PD deficiency was less, the result cannot be generalized.

Conclusion

The study demonstrates the wide spectrum of clinical presentation of malaria in the pediatric population. There may be geographic variation in clinical presentation and few complications, MODS, which are thought to be common in the adult population are not uncommon in the pediatric population. Presence of respiratory distress, CNS involvement, renal failure, shock are independent predictors of mortality in pediatric patients with severe malaria. Multiorgan dysfunction is not rare in the pediatric population, and is an independent predictor of mortality.

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