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Original Research Article

Clinical Manifestation and Predictors of Mortality in Severe Malaria in Children

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Abstract: The objective of present study is to recognizing risk factors those are associated with poor outcome in children with severe malaria. **A** Prospective observational study was set in Pediatric Intensive Care Unit of tertiary care hospital. A 170 cases of severe malaria between the age group of 6 months to 12 years of either sex with confirmed slide positivity for malaria parasite who satisfied WHO 2000 criteria for severe malaria were enrolled, after approval from institutional ethical committee and parent's informed consent. Detail clinical evaluation was done including assessment of various risk factors like respiratory distress syndrome, multiorgan dysfunction, hypoglycemia, jaundice, renal failure, impaired conscious, cerebral malaria, spontaneous bleeding, hyperparasitemia, shock and severe anaemia**.** Case fatality ratio was 19.4% and maximum in the age group between 6 months to 2 years. A MODS was most significant variable associated with poor outcome followed by shock, coma and bleeding tendency. MODS, shock, cerebral malaria and bleeding tendency are significant variable predicting poor outcome with severe malaria.
Keywords:ARDS, Cerebral malaria, Hyperparasitemia, Multiorgan dysfunction, severe malaria, Shock

INTRODUCTION

Malaria is one of the commonest potentially life threatening infection. Globally more than 1 million deaths occur per year, about 60% of clinical episode and more than 80% deaths occur in young children [1]. Plasmodium falciparum causes the most severe form of disease, without early diagnosis and prompt case management case fatality is very high especially in young children. The situation is getting complicated by the increasing chloroquine resistance in the parasite in many years [2]. The main objective of treatment of severe malaria is to prevent death. The mortality of severe untreated malaria is thought to approach 100%, with prompt early effective treatment mortality falls to 15-20% [3].Despite of introduction of more rational antimalarial regimen in recent years and increasing use of most rapidly parasiticidal artemisinin derivative, mortality has not significantly reduced[4,5]. Since severe malaria is a serious disease associated with unfavorable outcome, a system must be present to assess the disease severity and to estimate the probability of mortality amongst patients. This will help clinicians to communicate with parents as well as to compare effect of various interventions. Outcomes in severe malaria depend on nature and degree of vital dysfunction. Present study aims to recognize risk factors that are associated with poor outcome in children with severe malaria. Understanding of these risk factors will provide additional understanding course of severe malaria and eventually lead to improved case management.

MATERIAL AND METHODS

Present prospective observational study was carried out in pediatric intensive care unit at Government Medical College Nagpur, one of the largest tertiary care referral hospitals of central India. Sample size was calculated using alpha error 10% with power of 75%. 170 cases of severe malaria, of age group between 6 months to 12 years of either sex were enrolled after obtaining informed consent from parents and approval from institutional ethical board. Cases were defined as confirmed slide positivity for malarial parasite and those who satisfied WHO 2000 criteria for severe malaria. Subjects who died within one hour of admission and suspected cases who were not slide positive were excluded. Detail clinical evaluation was done. Risk factors like respiratory distress, MODS, hypoglycemia, jaundice, renal failure, impaired consciousness, cerebral malaria, spontaneous bleeding, hyperparasitemia, shock, severe anemia were studied. Both thick and thin peripheral smear was prepared from finger prick examine for parasite and its type. Parasite density was calculated as number of parasite per 200

leukocytes on thick film and converted into parasite per microliter based on WBC count. Thin smear was stained with Leisaman and Giemsa stain for species identification. Other investigations like blood sugar, liver function test, kidney function test, CBC, coagulation profile, chest X-ray, ultra sound abdomen were carried out in all subjects.

Statistical Analysis

Data was collected in structural data sheet. Continuous variable were presented as mean± SD. Categorical variables were express in actual numbers and percentage. Chi square test was used for calculating P value. P<0.05 was considered as significant. Risk factors associate with poor outcome were identified using univariate analysis. Multiple logistic regression analysis was performed to evaluate independent effect of risk factors in predicting poor outcome.

RESULTS

In this study 170 cases of severe malaria with mean age was 7.32 years, maximum no of cases 43(25.5%)were in age group 10-12 years. There were 93(54.7%) males and 77(45.3%) female. Overall case fatality ratio was 19.4%, highest in age group 6 months to 2 years (23.5%).A 65.5% cases were from rural areas and 34.7% from urban areas.

A 105 (61.8%) cases were positive for Plasmodium falciparum case fatality ratio was 23% while 65 (38.2%) were positive for Plasmodium vivax and case fatality ratio was13.8%. A 100% cases were presented with fever, 66.47% with altered consciousness, 34% with convulsion, 22.9% with breathlessness, and 22.11% with headache, 19.4% with nausea and vomiting, 18.25% with jaundice and 7% with oligourea.

Splenomegaly was most clinical sign present in 97.64% cases followed by hepatomegaly in 51.7%, pallor in 38%, and icterus in 34% and edema in 24% cases.

On univariate analysis, variable like hypoglycemia, MODS, bleeding tendency, hemoglobinuria, ARDS, shock and coma were highly significant variable associate with poor outcome while impaired consciousness, convulsions, hyperparasitemia, Hemoglobinuria were significant variable associated with poor outcome (Table 1).

On multiple logistic regression analysis MODS to be most significant predictor followed by shock, coma and bleeding tendency of poor outcome in severe malaria (Table 2).

Of 42 cases of coma, 13 cases also had MODS. Case fatality ratio for coma was 61.9%, when coma and MODS both were present mortality was 100%. In 21 cases of severe malaria had bleeding tendency with case fatality ratio 66.7%, 8 cases among them had MODS and mortality among these combined cases was 100%. In 47 cases of shock in present study, 12 cases had MODS and case fatality ratio for shock was 55.3%. Mortality increased to 100% when bleeding tendency and MODS present together.

Table 1: Univariate analyses of various variables associated with poor outcome

Variables	P value
Impaired consciousness	0.018
Coma	<0.001
Convulsions	0.019
Severe Anemia	0.185
Jaundice	0.622
Shock	0.001
Hyperparasitemia	0.024
Acute Renal Failure	0.071
Gastrointestinal Dysfunction	0.491
Malnutrition	0.155
Hypoglycemia	<0.001
ARDS	<0.001
Hemoglobinuria	<0.010
Bleeding Tendency	<0.001
MODS	<0.001

Table 2: Multiple logistic regression analysis for predictors associate with poor outcome with severe malaria

Variables	OR	95% C I	P value
Convulsions	0.718	0.064-8.015	0.788
Bleeding tendency	0.028	0.001-0.701	0.029
Shock	0.029	0.003-0.293	0.003
Impaired consciousness	2.222	0.085-58.35	0.632
Coma	0.025	0.001-0.438	0.012
Hypoglycemia	0.047	0.002-1.314	0.072
ARDS	0.318	0.002-43.712	0.648
Hyperparasitemia	0.422	0.062-2.883	0.379
MODS	0.026	0.001-0.546	0.014

DISCUSSION

Malaria is one of the commonest potentially fatal infections in the World. India contributes to 75-77% of the total malaria in South East Asia. Most death occurs in young children living in areas of intense transmission of plasmodium falciparum and the commonest potential fatal syndrome being cerebral malaria. Study on factors associated with increased risk of developing severe malaria and death may provide additional understanding of course of disease and eventually lead to improve case management.

In present study, 73% cases were above the age group of five years and maximum (25.3%) were in age group of 10-12 years with mean age 7.32 years with male to female ratio of 1.2:1.Such age and sex distribution pattern were reported by Satpathy *et al* and Kumar *et al* [6,7]. A 65.30% cases were from rural area and 34.70% from urban area in present study. A study conducted by Govotechan *et al* [8] was reported malaria incidence is five times higher in rural area than urban.

Overall case fatality ratio was 19.4% and the gender wise mortality was 26.90% in male and 10.40% in female. The maximum case fatality was seen in the age group of 6 months to 2 years (23.5%). Case fatality ratio of 23% was seen in Plasmodium falciparum and 13.8% among cases with plasmodium Vivax infection. A similar study conducted by Yadav et al [9] reported case fatality of 7% with falciparum and 3% with Vivax infection.

All children in present study were presented with fever followed by altered sensorium (66.47%), convulsion (34%), breathlessness (22.9%), and headache (22.11%), nausea and vomiting (19.4%), jaundice (18.23%) and decrease urine output in 7% cases. A study conducted by Gohiya et al [10], fever was common presenting symptom in 98% cases.

Vomiting, altered sensorium convulsion, breathlessness, and headache and bleeding tendency in decreasing order while Peter *et al* [11] reported that altered sensorium was in 45%, reduced urine output in 35% and vomiting in 25% cases. A similar study conducted by Tripathy R *et al* [12] revealed that coma was most common clinical features followed by convulsion, impaired consciousness, jaundice, oligourea and breathlessness.

Splenomegaly was the most common (97.64%) clinical sign in our study followed by hepatomegaly (51.7%), pallor (38%), icterus (34%) and edema (24%) cases. A study done by Gohiya P *et al* reported splenomegaly in 65% and hepatomegaly in 57% cases in their study.

Predictors which are independently associated with risk of death are coma, multiorgan dysfunction, acute respiratory distress syndrome, spontaneous bleeding, hypoglycemia, shock, impaired consciousness and convulsions.

Cerebral malaria (coma) was present in 24.7% cases with case fatality ratio of 61.9%and had strong correlation of poor outcome (P<0.001) in our study. Tripathy *et al* reported that presence of cerebral malaria in 42% of cases with case fatality ratio of 60%, suggestive of strong correlation for poor outcome while Mockenhaupt *et al* [13] reported lesser (17%) cases of cerebral malaria and one of the variable of poor outcome.

Multiorgan dysfunction was one of the key predictor of poor survival and 100% case fatality ratio (P<0.001). Similar observation were made by Mockenhaupt *et al* and Tripathy *et al.* Acute respiratory distress syndrome was another presenting syndrome associated with 81.2%case fatality ratio (P<0.001) and was highly significant variable associated with poor outcome. Marsh *et al* [14] observed similar association in their study.

Shock was one of the predictor associated with poor outcome. It was observed in 27.64% cases with case fatality ratio of 55.3% (P<0.001). Gehlwat *et al*[15] reported shock in 16.7% cases and was found to be associated with poor outcome and similar finding are also reported by von Seidlein *et al* [16]. Hyperparasitemia was seen in 29.4% cases with case fatality ratio of 30%and was one of strong predictor of poor outcome. Similar finding were reported by Kumar et al and Tripathy *et al*. Bleeding tendency were observed in 12.35% cases with case fatality ratio of

66.75 (P<0.001) and was associated with poor outcome. Verma *et al* [17] reported spontaneous bleeding in 6% of cases and was associated with poor outcome.

Hypoglycemia was revealed in 7% cases with case fatality ratio of 91.7%and strongly correlate with poor outcome (P<0.001). A study done by Tripathy *et al* reported hypoglycemia in 6% cases with strong prediction of poor outcome. Convulsions were observed in 34.11%cases with case fatality ratio of 29.3% while hemoglobinuria in 17% cases with case fatality ratio of 43.3% and both was significantly associated with poor outcome (P<0.001). Similar correlations were reported by Satpahyta *et al*, Oluwayemi *et al* [18].

Present study also showed severe anemia, jaundice, malnutrition and gastrointestinal dysfunction are not useful variables for predicting poor outcome. The estimated prevalence of acute renal failure in this study was 7.64% and was not found to be helpful in predicting poor outcome. Aggressive case management of acute renal failure in this study probably helps to improve survival. But Padhi Rk *et al*[19] reported adverse outcome in cases of severe malaria with renal involvement.

Analysis of data using multiple logistic regressions showed multiorgan dysfunction, shock, bleeding tendencies and coma are significant variable in predicting poor outcome among cases with severe malaria.

CONCLUSION

Severe malaria is a major problem affecting health of children in India. Presence of multiple complications has made management difficult and challenging. To predict survival of cases of severe malaria is difficult and demanding for treating physician. Therefore there is need to identify factors that would be helpful in predicting poor outcome among cases of severe malaria that can be used even in peripheral hospital to predict outcome. In present study multiorgan dysfunction, cerebral malaria, shock and bleeding tendencies have emerged as important risk factors that predict poor outcome among cases of severe malaria.

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