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Original Research Article

Evaluation of complications and factors associated with multi-organ dysfunction in malaria: a cross sectional study

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ABSTRACT

Background: Prevalence of complications in malaria continues to grow even with reducing number of malaria cases. Complications associated with malaria can involve multiple organs. There is paucity of literature on factors associated with multi organ dysfunction in different types of malaria.
Methods: Our aim was to study the clinical profile of complications in different types of malaria with specific focus on multi-organ dysfunction (MODS). In this cross-sectional study confirmed cases of malaria were enrolled.
Results: *Plasmodium vivax* malaria was the predominant type seen in 74.1% cases. The overall prevalence of thrombocytopenia was 61.5%, hepatic dysfunction 58%, cerebral malaria 16.1%, Hypoglycemia 7.5%, bleeding 34.5%, acute respiratory distress syndrome (ARDS) 5.7% and acute kidney injury (AKI) 49.4%. Hypoglycemia was significantly higher in mixed malaria (0.025, p = 0.025). Hepatic dysfunction and hyperbilirubinemia were significantly higher in mixed malaria (p=0.001). Mortality was seen in mixed malaria (p = 0.007). Only those with mixed malaria died (13%). Patients with MODS had higher prevalence of rashes (p <0.0001) and cerebral malaria (p = 0.000). Serum levels of urea, creatinine, Bilirubin, Serum glutamic oxaloacetic transaminase (SGOT) and Serum glutamic pyruvic transaminase (SGPT) were significantly higher in patients with MODS (p<0.0001 for all variables). On evaluating factors associated with multi-organ dysfunction presence of cerebral malaria [OR: 6.4 (95% CI): 2.4 to 17.4; p<0.0001], type of malaria (Vivax or Falciparum or both) [1.77 (1.03 to 3.03); p=0.0038], and hypoglycemia [4.4 (1.08 to 17.8); p=0.038] were statistically significant on multivariate analysis.
Conclusions: The present study demonstrates the factors associated with multi organ dysfunction and its impact on clinical outcome in different types of malaria.

Keywords: Cerebral malaria, Hyperbilirubinemia, Mixed Malaria, Multi organ dysfunction

INTRODUCTION

Malaria is one of the most important health problem caused by parasites in human. According to the WHO (World Health organization) report of 2016 there were an estimated 216 million cases of malaria distributed in 91 countries and number of patients succumbing to malaria was estimated to be 445000. South East Asian Region contributes the second maximum number of malaria (10%) next only to African region (88%).[1] Complicated malaria can involve various organ systems including the respiratory, hematological, CNS (central nervous system), renal and hepatic. The observed prevalence of various complications in malaria varies with the region

and endemicity as well as the resistance pattern to the various drugs available for the treatment. Multi organ dysfunction can occur in complicated malaria. The Prevalence of multi organ dysfunction ranges from 20 -65 % in various studies.[2,3]

However, inspite of occurrence of multi organ dysfunction there is paucity of data on its impact on various other complications of malaria like thrombocytopenia, hypoglycemia, ARDS, AKI and cerebral malaria and the clinical outcome.

There are very few studies on factors associated with MODS in different types of malaria. In this study apart from studying the clinical profile and complications, authors aimed to evaluate the impact of multi organ dysfunction on thrombocytopenia, hypoglycemia, ARDS, AKI and cerebral malaria and clinical outcome. Authors also evaluated the factors associated with MODS in different types of malaria.

METHODS

It was a cross sectional study conducted at a tertiary care teaching Hospital in North India.

All confirmed malaria cases by antigen method and age≥14 years were included in the study. A total of 174 patients were enrolled for the study. Authors excluded other causes of fever, hepatic dysfunction, thrombocytopenia, ARDS, hypoglycemia, AKI and meningo-encephalitis by appropriate history, clinical examination and investigations.

Authors also excluded those on medications which influence the hepatic function. The exclusion criteria were carefully looked for in the enrolled subjects. The eligible subjects were enrolled after obtaining written informed consent. The study was approved by the Institutional Ethics Committee.

Present objectives were to evaluate the prevalence of various complications in malaria, to study the prevalence of multi organ dysfunction in different types of malaria and to study the factors associated with multi-organ dysfunction in malaria.

Once enrolled a detailed history and clinical examination was performed and the variables were recorded in a pre-structured proforma. The diagnosis of malaria was made using the Rapid diagnostic test by detection of malaria antigen i.e. HRP-2 (Histidine Rich Protein-2) for Plasmodium Falciparum and Lactate dehydrogenase (LDH) for *Plasmodium vivax* and peripheral smear examination of malarial parasites. The subjects also underwent routine investigations which included the complete haemogram, liver function tests, kidney function tests, Hepatitis B antigen, Hepatitis C antibody,chest X-ray, sonography of abdomen and Arterial blood gas in case of suspected ARDS. Other causes of fever were ruled out using appropriate investigations.

Statistical analysis

Data of all the enrolled patients were collected in a standard proforma and entered in Microsoft Excel 2007. Statistical analysis was performed using Stata 11.2 (Stata Corp, College Station, TX). Chi-square test was used to compare the categorical variables while Student's t-test or Wilcoxon rank sum test was used for continuous variables. P value of < 0.05 was considered significant.

For determining the factors associated with multi-organ dysfunction, authors performed univariate analysis followed by multivariate logistic regression using presence of MODS as the dependent variable and all others as independent variables.

RESULTS

The baseline characteristics of the enrolled subjects are described in the Table 1. A total of 174 subjects were enrolled for the study. P. vivax was seen in 74.1 %, P. falciparum in 17.24% and both in 8.62%. The mean (SD) age was 34 years in P. vivax and 35 years in P. falciparum and mixed malaria.

Males were in majority with 65.5% of all subjects. The mean hemoglobin and total leucocytes were comparable in all three types. The median platelet count was lower in mixed malaria with 56000/µ lit Vs 72000/µ lit in P. vivax and 81,000/µ lit in P. falciparum.

The mean blood urea was significant higher in mixed malaria at 83 mg/dl (p=0.03). Serum creatinine was significantly higher in mixed malaria at 2.4 mg/dl (p=0.001). Indirect and direct bilirubin were also higher in mixed malaria with p=<0.0001 and 0.0009 respectively.

SGOT and SGPT levels were also higher in mixed malaria with p=0.004 and 0.0002 respectively. The occurrence of rashes and splenomegaly were similar in all three types.

Various complications in the study in different types of malaria are described in Table 2. Prevalence of bleeding episodes was 34.5% whereas hypoglycemia was seen in 7.5% cases. Thrombocytopenia was seen in 61.5% patients.

Renal dysfunction was seen in 49.4% whereas hepatic dysfunction was seen in 58% subjects. Cerebral malaria was seen in 16.1% and ARDS in 5.7%. Death was seen in 1.1% patients.

Table 1: Comparison of baseline characteristics of those with P. vivax, P. falciparum and co-infection with both.

Variables	P. vivax (n=129)	P. falciparum (n=30)	Both (n=15)	P-value
Age (Years); mean (SD)	34 (14)	35 (13)	35 (16)	0.81
Male (%)	81 (63%)	24 (80%)	9 (60%)	0.18
Hemoglobin (gm/dl), mean (SD)	11.4 (1.8)	12 (2)	11 (2)	0.56
TLC(/µL), mean (SD)	7017 (2282)	8030 (2918)	7920 (2520)	0.15
Platelet count(/µL), median IQR	72000 (40000, 180000)	81000 (43000, 160000)	56000 (27000, 176000)	0.19
Blood urea (mg/dl), mean (SD)	54 (26)	64 (29)	83 (33)	0.03
Serum creatinine (mg/dl), mean (SD)	1.5 (0.7)	1.8 (1)	2.4 (1)	0.001
Total bilirubin (mg/dl), median IQR	1.3 (1, 2.5)	1.5 (0.9,2.7)	3 (2.8, 4.1)	0.03
Indirect bilirubin (mg/dl), median IQR	0.40 (0.3, 0.7)	0.4 (0.3, 0.9)	1.2 (1, 1.2)	<0.0001
Direct bilirubin (mg/dl), median IQR	1 (0.7,1.8)	1.2 (0.7, 1.8)	2 (1.6, 2.9)	0.0009
SGOT (IU/L), median (IQR)	34 (23,77)	42 (20, 86)	88 (70,103)	0.004
SGPT (IU/L), median (IQR)	34 (24,59)	38 (24, 76)	81 (65, 98)	0.0002
Rashes	55 (43)	11 (37)	8 (53)	0.56
Splenomegaly	21(16%)	6 (20%)	3 (20%)	0.74

Table 2: Profile of complications in different types of malaria.

Variables	Overall prevalence n (%)	P. vivax n (%)	P. falciparum n (%)	Both n (%)	P-value
Bleeding	60 (34.5%)	42 (33%)	11 (37%)	7 (47%)	0.53
Hypoglycaemia	13 (7.5%)	7 (5.4%)	2 (6.7%)	4 (27%)	0.025
Anaemia	124 (71.3%)	92 (71%)	20 (67%)	12 (80%)	0.65
Thrombocytopenia	107 (61.5%)	78 (60%)	19 (63%)	10 (67%)	0.87
Acute kidney injury	86 (49.4%)	58 (45%)	17 (57%)	11 (73%)	0.08
Hepatic Dysfunction	101 (58%)	69 (53%)	17 (57%)	15 (100%)	0.001
Hyperbilirubinemia	99 (56.9%)	68 (53%)	16 (53%)	15 (100%)	0.001
Cerebral malaria	28 (16.1%)	16 (12%)	9 (30%)	3 (20%)	0.05
Acute respiratory distress syndrome	10 (5.7%)	8 (6.2%)	0	2 (13%)	0.16
Death	2 (1.1%)	0	0	2 (13%)	0.007

Prevalence of hypoglycemia was 27% in mixed malaria as compared to 5.4% and 6.7% in P. vivax and P. falciparum respectively (p=0.025).

The prevalence of anemia, thrombocytopenia, AKI, cerebral malaria and ARDS were similar in all three types.

Hyperbilirubinemia was seen in all patients with mixed malaria as compared to 53% in *P. vivax* and *P. falciparum* (p=0.001).

Hepatic dysfunction was seen in all cases of mixed malaria whereas the prevalence was 53% in *P. vivax* and 57% in *P. falciparum* (p=0.001). Two deaths in the study had mixed malaria (p=0.007).

Factors associated with multi-organ dysfunction are described in Table 3. Rashes were seen in 61% cases with multiorgan dysfunction versus 28% without multi organ dysfunction (p=<0.0001). 29% of patients with MODS had cerebral malaria as compared to 6% in patients without MODS (p=<0.0001).

Median platelet count was significantly lower in patients with MODS 45000/µ lit versus 1,60,000/µ lit (p<0.0001). Serum creatinine was significantly higher in MODS with values 2.16mg/dl versus 1.06mg/dl (p<0.0001).

Serum bilirubin and SGOT, SGPT levels were also higher in patients with MODS (<0.0001). The two patients who died had multiorgan dysfunction.

On evaluating factors associated with multi-organ dysfunction presence of cerebral malaria [OR: 6.4 (95% CI): 2.4 to 17.4; p<0.0001], type of malaria (vivax or falciparum or both) [1.77 (1.03 to 3.03); p=0.0038], and hypoglycemia [4.4 (1.08 to 17.8); p=0.038] were statistically significant on multivariate analysis.

Table 3: Factors affecting multi organ dysfunction in malaria.

Variables	Multiorgan dysfunction present	Absent	P-value
Age (Years); mean (SD)	35 (14)	33 (14)	0.4
P. vivax n (%)	61 (79%)	83 (86%)	0.27
P. falciparum n (%)	27 (35%)	18 (19%)	0.01
Anaemia, n (%)	53 (69%)	71 (73%)	0.52
Male n (%)	30 (39%)	30 (31%)	0.26
Rashes n (%)	47 (61%)	27 (28%)	<0.0001
Cerebral malaria n (%)	22 (29%)	6 (6%)	<0.0001
Hemoglobin (gm/dl), mean (SD)	11.3 (2)	12 (2)	0.42
Mortality n (%)	2 (2.6%)	0	0.19
TLC/µL, mean (SD)	7175 (2341)	7344 (2535)	0.65
Platelet count/ µL, median IQR	45000 (30000, 78000)	160000 (60000, 200000)	<0.0001
Blood urea mg/dl mean (SD)	78 (25)	43(19)	<0.0001
Serum creatinine mg/dl mean (SD)	2.16 (0.80)	1.06(0.45)	<0.0001
Total Bilirubin mg/dl median IQR	2.6 (2, 3.1)	1.1(0.9, 1.6)	<0.0001
Indirect Bilirubin mg/dl median IQR	0.7 (0.5, 1.1)	0.3 (0.3, 0.4)	<0.0001
Direct Bilirubin mg/dl, median IQR	1.8 (1.3,2.1)	0.7 (0.7,1.1)	<0.0001
SGOT IU/L, median (IQR)	78 (55, 96)	30 (20, 38)	<0.0001
SGPT IU/L, median (IQR)	69 (46, 85)	28 (22, 38)	<0.0001

DISCUSSION

Significant research has been done to elucidate the biological basis of complications and multi organ dysfunction in malaria. Plasmodium Vivax which was initially thought to be benign type of malaria is now increasingly associated with complications and MODS. Involvement of multiple organ system can occur in different types of malaria which may be attributed to the endemicity in the region and the parasite burden in the infected. Various pathogenic mechanisms have been studied in detail to understand the mechanism of involvement of various organs in complicated malaria. In this study authors have tried to study the profile of complications in different types of malaria and understand the various factors associated with MODS and their impact on clinical outcome.

Present study observed splenomegaly in 17.24% cases which is in contrast to the study by Goyal JP et al which reported the incidence to be 44%.[4] The lower prevalence of splenomegaly may be due the different age groups in the study. Present study had adult patients where as in the study by Goyal JP it was the pediatric group.

In present study overt bleeding was seen in 34.5% in contrast to that reported by Balaraju G et al (3.33%).[5] The higher incidence of bleeding episodes may be due to delayed presentation to the hospital and lower levels of platelet count in present study as thrombocytopenia was seen in 61.5% cases.

In this study, hemoglobin (Hb) levels were reduced in the patients with malaria as compared to the healthy subjects reported in various studies. This finding is similar to other studies.[6,7] Various other studies have reported a reduction in hemoglobin concentration in patients with malaria parasitemia. In this study the mean hemoglobin concentration was 11.46 g/dL, but, in the study done by Nadeem et al, hemoglobin level in P. falciparum affected patients was 13.7 gm/dL.8 The Reduced hemoglobin in malaria may be attributed to the increased destruction of red blood cells by the malarial parasites.[9,10]

In present study, thrombocytopenia was commonly associated with malaria infection which is similar to the observation in various other studies.[7,11,12] Low platelet count is a more frequent finding of malarial infection than anemia.

This study shows significant increase in liver enzymes SGOT and SGPT and bilirubin levels especially in the mixed type of malaria. The increased serum levels of liver enzymes and bilirubin suggest hepatic dysfunction. The results in present study are consistent with other studies which have reported elevation in liver enzymes and bilirubin levels indicating liver damage.[13,14] In malaria, raised bilirubin is mainly due to destruction of the parasitized red blood cells and damage to liver.[15]

Renal derangement was observed in 49.4% cases in present study. The renal dysfunction was observed in 73% in mixed malaria cases and 57% in P. falciparum malaria. The finding is similar to that reported by Misra DP et al who also observed raised serum creatinine in 57% cases of complicated falciparum malaria.[16] Multiple factors appears to be contributing to renal dysfunction malaria which includes microvascular obstruction caused by parasitized erythrocytes.[17] Apart from parasites, glycosylphosphatidylinositol a monocytic receptor

covalently binds to the surface antigens of falciparum malaria parasites and Stimulate monocytes to release the tumor necrosis factor, which in turn enhances synthesis of various pro-inflammatory mediators which causes vasodilatation and increases vascular permeability resulting in hypovolemia which contributes to ischemic renal failure.[18]

ARDS was seen in 5.7% cases overall and 13% of cases with mixed malaria. It is similar to that reported by Mishra et al 2005 who reported an incidence of 4.6% and 6.25% as reported by Chisti et al.[19,20] ARDS in malaria is attributed to release of pro-inflammatory mediators by the malaria parasite which leads to increased alveolar permeability.[21]

Cerebral malaria was seen in 16.1% cases in this study. Cerebral malaria prevalence has been reported to be between 22-40% in various studies.[22] Pathogenesis of cerebral malaria is attributed to the sequestration and cytoadherence of the malaria parasite which causes micro vascular obstruction which leads to coma and seizures.[23-26]

The overall prevalence of multi organ dysfunction was seen in 44.25% cases. This figure was much higher in mixed malaria at 80 % Where as it was 38.8% in P. vivax and 50 % in P. falciparum malaria. Jain et al had reported an incidence of 38% multi organ dysfunction in malaria where as Kochar et al had recorded 61% MODS among children in Rajasthan.[2,3]

On evaluating factors associated with multi-organ dysfunction presence of cerebral malaria [OR: 6.4 (95% CI): 2.4 to 17.4; p<0.0001], type of malaria (Vivax or falciparum or both) [1.77 (1.03 to 3.03); p=0.0038], and hypoglycemia [4.4 (1.08 to 17.8); p=0.038] were statistically significant on multivariate analysis

Thus, present study highlights the observation that occurrence of multi organ dysfunction is very high in cases of malaria. The dysfunction is all the more common in mixed malaria cases and is associated with increased mortality. Multivariate analysis also revealed significant independent association of cerebral malaria, types of malaria and hypoglycemia with multi organ dysfunction.

CONCLUSION

Malaria is an important treatable cause of multi organ dysfunction. In endemic areas malaria screening should be considered for all patents presenting with fever as well as associated complications. Early diagnosis and treatment can help to improve the outcomes of severe malaria patients and prevent organ damage which can be fatal at times. Early identification of type of malaria, hypoglycemia, cerebral malaria, Hepatic dysfunction, renal dysfunction may help in reduction of mortality and morbidity. Patients with multiorgan dysfunction should be managed on the lines of severe sepsis with a multi-disciplinary approach.

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