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A Study on Prognostic Value of Thrombocytopenia in Falciparum Malaria in Jharkhand

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Abstract
Introduction: *Falciparum malaria accounts for most of the deaths amongst the malaria cases. Severe falciparum malaria is infact a medical emergency and requires immediate management and intensive nursing care. It is prone to complications such as cerebral malaria, hypoglycaemia, acidosis, renal impairement, liver dysfunction etc. The haematological abnormalities that may be seen in P. falciparum malaria are anemia and thrombocytopenia. Thrombocytopenia could be an early marker of disease severity. The aim of our study was to study the incidence and prognostic value of thrombocytopenia in Plasmodium falciparum malaria.*
Material and Method: *This was an prospective observational study done on 80 admitted patients of falciparum malaria in Department of Medicine, Rajendra institute of medical science, Ranchi, Jharkhand.*
Results: *The total no. of case studied were 80(n=80). The mean age of patients were 34.72 ± 12.54 years. Majority of the cases (64) were seen in age group 20 -50 years (80%). On seeing the sex distribution, total no. of cases among male patients were 60(75%) and amongst females were 20(25%), no. of males was more than females. Majority of the cases were from rural areas 57(71.25%) as compared to urban areas 23(28.75%) which may be due to poverty, lack of proper education and living in unhygienic conditions. 31.25% of the patients (25) were tribal and 68.75 % (55) were non-tribals. Mild thrombocytopenia was seen in 16 patients (35.56%) of complicated malaria as compared to 15 patients (42.86%) of uncomplicated malaria. Moderate thrombocytopenia is seen in 22 patients (48.89%) of complicated cases as compared to 08 patients (22.86%) of uncomplicated malaria cases. Severe thrombocytopenia was observed in 06 patients, all patients (13.33%) were having complicated malaria and no patients of uncomplicated malaria had severe thrombocytopenia.*
Conclusion: *Amongst the various markers of falciparum malaria such as jaundice, anemia, splenomegaly, thrombocytopenia has emerged as the strongest predictor of falciparum malaria. The sensitivity of thrombocytopenia together with acute febrile syndrome was almost 100% for malarial diagnosis. Overall incidence of thrombocytopenia with falciparum malaria was 83.75%. Thromobocytopenia manifests before even anemia and splenomegaly sets in. Thus, it could help in early diagnosis of falciparum malaria so that antimalarial drugs could be initiated in time saving many lives. Thrombocytopenia is a marker of severe disease in falciparum malaria.*
Keywords: *Severe falciparum malaria, Haematological abnormalities, Thrombocytopenia.*

Introduction

Malaria has been a heavy burden in tropical countries like India since ages and it continues to be a major cause for morbidity and mortality with an estimated 445000 death in 2016.[1] Six species of plasmodium are responsible for causing diseases in humans. These are P. falciparum, P. vivax, two morphologically identical sympatric species of P. ovale, P. malariae, and P. knowlesi (the monkey malaria parasite in Southeast Asia). Plasmodium falciparum is the most notorious species to cause mortality. Infection starts with bite of female anopheles mosquito, which transmites plasmodial-sporozoites from its salivary gland in the blood stream. Sporozoites then invade the liver cells and begin to divide to produce daughter cells this process is known as intrahepatic or preerythrocytic schizogony. A single sporozoite produces 10000 to > 30000 daughter sporozoites which cause liver cells to swell and ultimately cause the cell to rupture, releasing the motile forms merozoites into the blood. These merozoites now invade fresh red blood cells (RBCs) and multiply every 48 hrs in P. falciparum and P. vivax, 24 hrs in P. knowlesi, and 72 hrs in P malaraie. Periodicity of fever of each species depend on this asexual cycle in erythrocytes. After invading RBCs, merozoites become trophozoites. It attaches to the red blood cells with the help of a specific surfacereceptor, for P. falciparum the reticulocyte-binding protein homologue 5 (PfRh5) is necessary for erythrocyte invasion. Basigin is the receptor of PfRh5. Duffy blood- group antigen Fy^a or $Fy^b$is the receptor for P. vivax infection. Duffy-negative FyFy phenotype is seen in West African population, thus they are seen to be resistant to P. vivax infection.

In P. falciparum infection, knobs appear on erythrocyte's surface 12-15 h after the cell invasion. These "knobs" are strain specific erythrocyte membrane adhesive protein (PfEMP1) which mediate attachment on venular and capillary endothelium- termed as cytoadherence. These sticky RBCs can cause blocking of capillaries and venules. Infected RBCs can also adhere to uninfected known as rosetting. They can also adhere to infected RBCs known as agglutination. Thus, cytoadherence, rosetting and agglutination are the central to the pathogenesis of falciparum malaria. They cause sequestration of RBCs (which contain mature form of parasites) in vital organs (specially brain) and interfere with the blood flow and metabolism. In this way sequestered parasites escape host defense like splenic processing and filtration. Sequestration is seen only in P. falciparum infection. So younger ring forms are seen in peripheral blood smear in falciparum malaria unlike other human malaria where all stages of parasites can be seen in peripheral blood.[2]

Anemia, thrombocytopenia and disseminated intravascular coagulation are the most common associated hematological complications in falciparum malaria.[1-8] Anemia in falciparum malaria could be due to intravascular haemolysis.[9] Thrombocytopenia is the common along with anemia in malarial infection. Anemia and thrombocytopenia subside gradually with therapy and with clearance of parasitemia. Factors involved in pathogenesis of thrombocytopenia include hypersplenism, destruction of platelets bound by immune complexes (PAIgG) by the reticuloendothelial system and Disseminated Intravascular Coagulation (DIC).[10] Patients infected with malaria bear an inverse relationship between the platelet counts and the platelet anti body level.[11] Thrombocytopenia is an early indicator for acute malaria, a finding that very frequent and present even before anemia and splenomegaly sets in. Thrombocytopenia in falciparum malaria is associated with high concentrations of IL-10, suggesting that platelets may play a role in the pathophysiology of severe malaria.[12]

Parenteral Artesunate is the drug of choice for severe malaria and it should be started as early as possible. It does not require dose adjustment in liver dysfunction or in renal failure. It can be given in pregnant women also. While antimalarial drug is the mainstay of treatment, in acute renal failure or severe metabolic acidosis haemodialysis is needed. Anemia is corrected with whole blood (preferably

fresh) or packed cell if haematocrit falls below 20%. Intravenous benzodiazepines are used for convulsion. A single dose of oral primaquine 0.75 mg/kg should be given in all cases of falciparum malaria for gametocidal action.

The early diagnosis of falciparum malaria is the key feature for its prompt treatment and prevention of complications such as coma, hypoglycaemia, jaundice, acidosis, renal failure or pulmonary oedema. Microscopic diagnosis is advocated for confirmation of diagnosis of malaria but it requires technical expertise and at times may be unreliable when poorly executed.[1] Certain haematological changes which include low platelet count, haemoglobin concentration and hematocrit have been reported to be associated with malaria in few studies.[13,14] Recently many studies have been conducted to analyze the role of platelet indices to discriminate various causes of thrombocytopenia and its association with severity of p. falciparum malaria.[15] Jharkhand is amongst the malaria endemic states of India with few studies. The study was therefore conducted to analyze the prognostic value of thrombocytopenia in patients of falciparum malaria.

Material and Methods

A hospital based prospective observational study was done on 80 admitted patients of P. falciparum malaria admitted in department of medicine in our hospital from July 2017 to September 2018 after taking informed consent from the patient or attendant. The approval of institutional ethics committee was taken prior to the commencement of this study. A case sheet proforma was prepared and data regarding demographic profile, clinical features, investigations, treatment, and complication were recorded. Severe falciparum malaria was diagnosed as per guidelines of WHO.[16]

Inclusion criteria:- Only those cases whose blood were found to be positive for Plasmodium falciparum by peripheral blood smear examination under microscope or antigen test were considered for this study.

Exclusion criteria: Patients with Pre-existing neurological disease, Pre-existing haematological disease, Pre-existing acute or chronic renal failure, Pre-existing liver disease were excluded from study.

Two groups were studied, one had the patients with features of uncomplicated malaria and other group had the patients with clinical features of complicated Plasmodium falciparum malaria.

Group I– Uncomplicated P. falciparum malaria (n=35): Common presenting complaints in this group were fever with chills, headache, fatigue, abdominal discomfort, muscular ache, nausea, vomiting, mild anemia and a palpable spleen in few cases.

Group II– Complicated or severe P. falciparum malaria (n=45):This group of patients presented to the hospital with severe manifestations such as cerebral malaria, severe normochromic, normocytic anemia, renal failure, pulmonary edema /adult respiratory distress syndrome (ARDS), hypoglycemia, hypotension/shock, bleeding/ disseminated intravascular coagulation, convulsions, hemoglobinuria, acidemia/acidosis, jaundice. These are life threatening complication that demand urgent attention.

The following investigations were done in cases under study:

1) Blood for TC & DC of WBCs, Platelet count, Hb% estimation.
2) Peripheral blood smear, both thick and thin for the presence of P.falciparum.
3) Rapid diagnostic kit test for P.falciparum.
4) Random blood sugar
5) Renal function test – Blood urea and serum creatinine.
6) Liver function test – Serum Bilirubin (Total, Direct and Indirect), SGOT, SGPT, alkaline phosphatase.
6) USG Abdomen – Only those cases with relevant findings suggestive of deranged renal function.

Statistical Analysis

Microsoft office 2010 was used for the statistical analysis in this study. Descriptive statistics like mean and percentages were used in the analysis of data.

Result

The total no. of case studied were 80(n=80) who were positive for P. falciparum malaria either by peripheral smear examination (thick and thin) or by malarial antigen test. The mean age of patients were 34.72 ± 12.54 years. Majority of the cases (64) were seen in age group 20 -50 years (80%). On seeing the sex distribution, total no. of cases among male patients were 60(75%) and amongst females were 20(25%), no. of males was more than females. Majority of the cases were from rural areas 57(71.25%) as compared to urban areas 23(28.75%) which may be due to poverty, lack of proper education and living in unhygienic conditions. 31.25% of the patients (25) were tribal and 68.75 % (55) were non-tribals.

Fever was the commonest clinical presentation with chills and rigors. It was seen in 100% of patients followed by neck rigidity in which was seen in 55% of patients. Altered sensorium was observed in 26.25%(21) followed by jaundice in 25%(20) of patients. Acute renal failure was seen in 20% (16) of cases. Coma and convulsion were seen in 16.25% and 6.25% of cases respectively. Splenomegaly in 47.5% (38) cases & hepatomegaly in 36.25 %(29) cases. Severe anaemia was seen in 11.25%(09) of cases. Hypoglycaemia was seen in 5%(04) cases. One patient developed ARDS (Adult Respiratory Distress Syndrome). Acidosis was seen in 20%(16) of cases. Whereas hemoglobinuria and DIC were in 7.5% and 2.5% of cases respectively. (Table 1)

Table 1 clinical presentation seen in study cases

Clinical presentation	No. of cases (%)
Fever with chills	80(100)
Altered sensorium	21(26.25)
Neck rigidity	44(55)
Convulsion	05(6.25)
Coma	13(16.25)
Severe anemia	09(11.25)
Hypoglycaemia	05(6.25)
Oliguria/renal failure	16(20)
Jaundice	20(25)
ARDS	01(1.25)
Shock	04(5)
Hepatomegaly	29(36.25)
Splenomegaly	38(47.5)
Acidosis	16(20)
Hemoglobinuria	06(7.5)
DIC	02(2.5)

Table 2 showing thrombocytopenia in cases of falciparum malaria under study

Thrombocytopenia	Severity of malaria		Total (%)
	Complicated(45)	Uncomplicated(35)	
Mild (1.0 – 1.5 lakh)	16(35.56%)	15(42.86%)	31(38.75)
Moderate (0.5 – 1.0 lakh)	22(48.89%)	08(22.86%)	30(37.5)
Severe (< 0.5 lakh)	06(13.33%)	00	06(7.5)
Normal platelet count	01(2.22%)	12(34.29%)	13(16.2)
Chi-square (χ^2) = 20.95, P = 0.0001(s)			

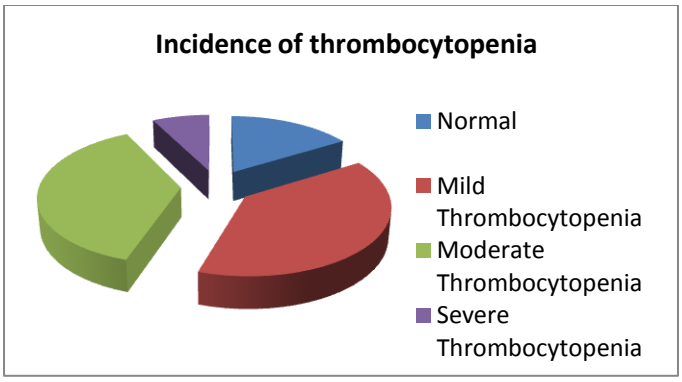
In our study, the association of thrombocytopenia with severity of malaria was observed. Overall incidence of thrombocytopenia in falciparum malaria was 83.75%. indicating a definite correlation of thrombocytopenia with falciparum malaria. Out of 80 patients, complicated malaria was seen in 45 patients and uncomplicated malaria was seen in 35 patients. Mild thrombocytopenia was seen in 16 patients (35.56%) of complicated malaria as compared to 15 patients (42.86%) of uncomplicated malaria. Moderate thrombocytopenia is seen in 22 patients (48.89%) of complicated cases as compared to 08 patients (22.86%) of uncomplicated malaria cases. Severe thrombocytopenia was observed in 06 patients, all patients (13.33%) were having complicated malaria and no patients of uncomplicated malaria had severe thrombocytopenia.

Table 3 Outcome of patients under study.

Malaria cases	Outcome		Total
	Recovered	Died	
Complicated	40	05	45
Uncomplicated	35	0	35

The outcome of patients with thrombocytopenia in relation complicated and uncomplicated falciparum malaria is shown in Table 3 above. Out of total 80 patients with thrombocytopenia, 75 patients (93.75%) recovered and 5 patients (6.25%) had mortality. Regarding complication related outcome, out of 45 patients with complicated falciparum infection 40(88.89%) showed recovery, 5 (11.11%) patient died.

Figure 1 Showing incidence of thrombocytopenia in the study.



Discussion

In this study, out of 80 patients (64) 80% patients were in age group between 20-50 years and with (31) 38.75% of patients in between 20 to 30 yrs of life which correlates with the observation done by Talib VH et al.[17] due to increase movement in young adults. The number of males (60)75% was more than females (20)25% in our study correlating with study conducted by Talib VH et al.[17] due to the increased outdoor activities and hence proximity to the mosquitoes. More of people coming from rural areas (71.25%) were infected with falciparum malaria as compared to urban areas (28.75%). This may be due to the fact that most of the villages in our country lack good health facility. By the time disease is diagnosed at primary health care centres (PHCs) most of the cases have developed severe complications. They are then reffered to tertiary care centres. Delay in referral of falciparum malaria cases may cost patient's life. Fever was the commonest clinical presentation with chills and rigors seen in 100% of patients. Headache was the 2nd most common symptom found in about 38% of patients which correlated with incidence of 33.40% in a study by Murthy GL et al.[18] and 33.45% in Mehta SR et al. The studies conducted by Mehta SR et al.[19] and Talib VH et al.[17] showed incidence of nausea and vomiting by 84.4% & 57.7% respectively in our study its incidence was 36%.

Jaundice was seen in 25% of patients which correlated with incidence of 23.41% in study by G. Lalitha Murthy et al.[18] In this study commonest sign was splenomegaly found in 38% of patients followed by anemia found in 11.25% of patients. In this study out of 80 patients, thrombocytopenia was observed in 67 (83.75%) of patients, which is similar to study of Jadhav UM et al. indicating thrombocytopenia is a common association in malaria,[20] majority being mild (38.75%) and moderate (37.5%) thrombocytopenia and severe thrombocytopenia <50000/µl in 06 patients and normal platelet count was noted in 16.25% of patients as per Table 2. which correlates with studies by Kumar and Sasirekha.[21] The sensitivity of thrombocytopenia together with the acute febrile syndrome was 100% for malaria diagnosis, with a specificity of 70%, a positive predictive value of 86% and a negative predictive value of 100%. In this study among 80 patients, 45 (23%) had complicated malaria and 35 (76.70%) had uncomplicated malaria. In this study, the association of thrombocytopenia with severity of malaria was observed. Severe thrombocytopenia was observed in 06 patients, all were associated with complicated malaria .

Conclusion

Falciparum malaria is a dreaded disease complicated by its atypical presentation. This cause delay in diagnosis and ultimately death of the patient. Various markers such as jaundice, anemia and splenomegaly may help in early diagnosis. Health education in rural areas and maintaining proper hygiene can further prevent the disease. Use of insecticides is essential for vector control. Other preventive measures such as bed nets, full sleeves clothing for males may protect them from mosquito bite. Elimination of mosquito breeding sites like stagnant water bodies should be encouraged among people.

Thus, we conclude that thrombocytopenia may be the most frequently associated hematological complication and has emerged as the strongest predictor of falciparum malaria. The sensitivity of thrombocytopenia together with acute febrile syndrome was almost 100% for malarial diagnosis. Thrombocytopenia is an early marker of

disease and could help in early diagnosis of this dreadful disease. However there were some limitations to the study like it was a single-centered study, sample size was small and duration of study was less, which might restrict the generalization of findings. A study over a longer period with bigger sample size would help in corroborating and generalizing the findings in future.

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