Original Research Article

A STUDY ON RELATIONSHIP OF THROMBOCYTOPENIA AND LIKELIHOOD OF SEVERE MALARIA IN PATIENTS ADMITTED WITH MALARIA IN A TERTIARY CARE HOSPITAL OF DAKSHINA KANNADA

ABSTRACT

Background: Malaria continues to be a huge socioeconomic burden despite various measures taken to curb the spread worldwide. It is also a global concern and more so in countries with a resource-limited setting. This inspired us to look at variables that could represent a severe disease in those limited settings, one such parameter being thrombocytopenia in malaria.

Aims and objectives

To find the relationship between thrombocytopenia and renal failure, hepatic dysfunction and cerebral malaria (severe malaria) and to identify if thrombocytopenia on the first day of admission increases the likelihood of severe malaria.

Methods

The study included 85 patients admitted in Yenepoya medical college hospital with fever and peripheral smear or malarial parasite fluorescent test (MPFT) positive for Plasmodium species.

Results

A total of 85 patients were included in the study. It was noted that the patients with profound thrombocytopenia (<20,000/μl) on day 1 were more commonly associated with manifestations of severe malaria-like cerebral malaria, renal failure, and jaundice. Platelet count of <50,000/μl was associated with increased incidence of renal failure, hepatic dysfunction, and cerebral malaria and increased mortality by an odds ratio of 4.37 on multivariate analysis

Conclusions

It was noted in our study that the presence of thrombocytopenia in a case of acute febrile illness increases the probability of malaria. This finding along with clinical suspicion of malaria should entail early treatment initiation. We have also noted that the presence of profound and severe thrombocytopenia was found to have a statistically significant correlation with cerebral malaria, renal failure and jaundice, and increased mortality.

Keywords: Malaria, Hepatic dysfunction, Renal impairment, Severe Malaria, Thrombocytopenia.

INTRODUCTION

Malaria continues to be a huge public health problem in many parts of the world. It remains an important cause of illness and death in developing countries.[1] Malaria is a global health problem with an annual incidence of 219 million cases of malaria worldwide, there was an estimated 435,000 malaria death worldwide in 2017 according to world Malaria report 2018.[2]The African region accounted for most of the global cases followed by South East Asian region and the eastern Mediterranean. In the south East Asian region of WHO, out of about 1.4 billion people living in 11 countries, 1.2 billion are exposed to a risk of malaria and most of this population live in India.[3] India contributes 75% of the total cases reported in South East Asia. About 2 million confirmed malaria cases and 1000 deaths are reported annually from India.[4]

In accordance with world Malaria report 2017, India accounted for 6% of all malaria cases in the world,6% of the death, and 51% of the global *P.vivax* cases. It estimates the total cases in India at 1.31 million and death at 23,990.[5] Maximum malaria cases in India are contributed by Orissa state. It contributes about 25% of total annual malaria cases, more

than 40% of *P.falciparum* malaria cases and nearly 20-30% of deaths caused annually. It is followed by Meghalaya, Mizoram, Maharashtra, Rajasthan, Gujarat, Karnataka, Goa, southern Madhya Pradesh, Chattisgarh and Jharkhand[6]

Severe malaria is common among tropical countries which are sometimes failed to be recognized. This might result in increased mortality rates secondary to severe malaria. Thrombocytopenia is one of the most common hematological complications. It increases the likelihood of malaria when present in acute febrile illness by almost 12 to 15 times.[7,8,9] The resource-limited setting of developing countries could lead to late recognition of severe malaria and hence result in increased mortality. This encouraged us to find ways that severe malaria could be recognized or suspected on day 1 of admission with a complete hemogram.

The aim of this study was to identify the significance of thrombocytopenia in malaria and its relevance as an early diagnostic tool in malaria. This study also aimed to correlate the severity of thrombocytopenia with various manifestations of severe malaria (renal impairment, hepatic dysfunction, cerebral malaria) to see whether initial platelet count could be used as a marker for severe malaria. Also, we looked at the relationship between thrombocytopenia in malaria and renal impairment, hepatic dysfunction, and cerebral malaria and mortality.

MATERIALS AND METHODS

The study was a prospective study conducted during the period from December 2016 to June 2018. We used convenience sampling to include 85 patients admitted in Yenepoya hospital meeting the inclusion criteria. The sample size was calculated as 85 with a level of significance 5%, the power of 80%. All patients admitted with acute febrile illness underwent malaria smear examination or rapid optimal test (MPFT). Those of the patients of age >18 years of age and with Plasmodium positive species identified by slide positivity and Rapid optimal test [MPFT] were included in the study. Patients having concomitant positive tests for dengue fever, leptospirosis, typhoid fever, and hepatitis B and C, HIV were not included in the study. Patients with chronic renal and liver disease were also excluded from the study.

Approval was obtained from the institutional ethics committee prior to the conduct of the study with protocol number 2016/346 on December 14, 2016. There were no ethical issues related to the study. The following investigations were done: Haemoglobin estimation, total WBC count and differential leucocytes count, platelet count, rapid diagnostic test (MPFT), Peripheral smear for malaria parasite, Random blood sugar, Liver function test, and Renal function test – Blood urea and S. creatinine. In selected cases arterial blood gas analysis, prothrombin time and activated partial thromboplastin time were done. Complications were defined according to WHO severity criteria for malaria.[10]

Table 1: Manifestations of severe malaria

Severe malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause, and in the presence of P. falciparum asexual parasitemia:

Impaired consciousness	A Glasgow Coma Score <11 in adults or a Blantyre coma score <3 in children
Acidosis	A base deficit of >8 meq/l or, if unavailable, a plasma bicarbonate of <15 mM or venous plasma lactate >5 mM. Severe acidosis manifests clinically as respiratory distress – rapid, deep and

	labored breathing
Hypoglycemia	Blood or plasma glucose <2.2 mM (<40 mg/dl)
Severe malarial anemia	A hemoglobin concentration <5 g/dl or a hematocrit of <15% in children <12 years of age (<7 g/dl and <20%, respectively, in adults) together with a parasite count >10 000/μl
Renal impairment (acute kidney injury)	Plasma or serum creatinine >265 μM (3 mg/dl) or blood urea >20 mM
Jaundice	Plasma or serum bilirubin >50 μM (3 mg/dl) together with a parasite count >100 000/μl
Pulmonary edema	Radiologically confirmed, or oxygen saturation <92% on room air with a respiratory rate >30/min, often with chest indrawing and crepitations on auscultation
Significant bleeding	Including recurrent or prolonged bleeding from nose gums or venepuncture sites; haematemesis or melaena
Shock	Compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitaemia	P. falciparum parasitemia>10%

Collected data was analyzed by descriptive and inferential statistical methods. Descriptive methods such as frequency and percentage were calculated to summarize the data of various parameters. Inferential methods such as Chi-square and Fischer's exact test were computed to find the significance of various parameters with outcome variables. The level of significance is 5% and analysis was performed using SPSS-17 software.

RESULTS

The study included 85 patients who were admitted at Yenepoya medical college hospital and were diagnosed as malaria by Malaria plasmodium fluorescence test or malaria parasite smear.

Out of 85 patients in the study, 69 were male and 16 were female. All the patients had a fever at presentation. The second most common presentation was headache. None of the patients had convulsions and only one patient had bleeding manifestations in the form of petechiae which resolved on its own. The demographic, clinical and laboratory features of the patients are outlined in Table 2.

It was noted that around 75(88.2%) patients had thrombocytopenia and was most commonly noted in *P.vivax* mono-infection in 49 patients(65.3%), followed by mixed malaria 17 patients (22.7%) and *P. falciparum* malaria 9 patients (12%). Profound thrombocytopenia with platelet count <20,000/μl was seen mostly in mixed (*P. vivax* and *P. falciparum*) and 1 case *of P. vivax* mono-infection.The most common range of thrombocytopenia was between 20000-50000/μl seen most commonly in vivax mono-infection.

In the present study, 27 patients had severe malaria meeting the WHO severity criteria. We concentrated mainly on renal impairment, hepatic dysfunction and cerebral malaria among the parameters used to define severe malaria. Out of 27 patients, 11 patients had renal failure, 20 patients had hyperbilirubinemia and 4 patients had cerebral malaria. In the current study, it was noted that renal failure had a significant correlation with severe and profound thrombocytopenia with higher mean creatinine values in patients with a low platelet count of <20,000/μl (p-value was 0.001 when Chi-square/Fischer exact test was applied). Higher mean bilirubin levels were noted with platelet count <20000/μl and was found to be statistically significant (p-value was 0.001 with Chi-square/Fischer exact test was applied) with low platelet count showing a p-value of 0.04 on Pearson correlation. The manifestation of cerebral malaria was seen in 4 patients in this study who had a low platelet count <50,000/μl at presentation.

TABLE 2: Demographic characteristics, symptoms, signs and lab features.

Patient Parameters	Value = N(% Of Total)
Age (In Years)-Mean	36.68
Men	69(81.2%)
Women	16(18.8%)
Fever(%)	85(100%)
Jaundice(%)	8(9.4%)
Headache(%)	56(65.9%)
Dyspnea(%)	8(9.4%)
Oliguria(%)	4(4.7%)
Bleeding Manifestations(%)	1(1.2%)
Altered Sensorium(%)	4(4.7%)
Convulsions(%)	0
Hepatomegaly(%)	23(27.1%)
Splenomegaly(%)	24(28.2%)
P. falciparum(%)	10(11.8%)

P. vivax(%)	57(67.1%)
Mixed(%)	18(21.2%)

Patient Lab Parameters and Clinical Profile	Values
Hemoglobin gm % (%)	
<7	20(4.7%)
7-11	61(23.5%)
Leucocyte count cells/cu mm(%)	
<4000	20(23.5%)
>11000	3(3.5%)
Platelet counts /μl (%)	
<20000	5(5.9%)
20000-50000	30(35.3%)
50000-100000	24(28.2%)
100000-150000	16(18.8%)
>150000	10(11.8%)
Cerebral malaria(%)	4(5%)
Metabolic acidosis Ph<7.24 and Hco3<15	5(6%)
Hyperbilirubinemeia serum bilirubin >3 mg/dl(%)	20(24%)
Renal failure(%)	11(13%)
Hypotension SBP<80 mmhg (%)	11((13%)

Table 3: Comparision of characteristics in patients who had mortality and survival as outcomes

Patient Characteristics	Patients with mortality (N=6)	Patients Who Survived(N=79)
Male	6	63
Female	0	16
Platelet count in cells/μl (mean+SD)	77833.33+130152.9	85734.18+78303.77
Serum creatinine in	5.88+3.71	1.05+0.42

mg/dl(mean+SD)		
Serum bilirubin in mg/dl(mean+SD)	16.28+15.008	2.32+1.87
Cerebral Malaria(N)	4	0

It is clear from table 3 that patients with lower platelet count, higher serum creatinine and higher serum bilirubin levels had higher mortality as against the patients who had normal or near normal values of these parameters. On multivariate analysis thrombocytopenia (<50,000/μl), hyperbilirubinemia and cerebral malaria increased the chances of severe malaria and mortality in patients with severe malaria by an odds ratio of 4.37.

Table 4: Univariate and Multivariate Odds Ratios of selected patient characteristics with mortality as an outcome

Patient Characteristics	N(% of total)	Univariate OR(95% CI)	Multivariate OR(95% CI)
Thrombocytopenia(<50,000/μl)	35(41.2)	8.16(0.91-73.30)	4.37(0.26-73.48)
Acute kidney injury(serum creatinine >3 mg/dl)	5(5.9)	-	
Hyperbilirubinemia(bilirubin>4mg/dl)	21(24.7)	19.68(2.14-180.55)	4.35(0.31-61.20)
Cerebral malaria	4(4.7)	78(6.15-989.03)	30.36(1.61-571.96)

DISCUSSION

The current study included 85 patients of malaria from Karnataka predominantly from Dakshina Kannada area.

Complications in severe malaria are either related to sequestration like ARDS, hepatic dysfunction, cerebral malaria, and renal dysfunction or non-sequestration related like anemia and thrombocytopenia. The sequestration-related complications are noted in *P.falciparum* infection but may not be visible on peripheral blood films due to heavy sequestration.[11] In the present study, severe thrombocytopenia with platelet range of 20,000-50,000 cells/μl was noted in 35.3% cases and profound thrombocytopenia with counts <20,000/μl was seen in 6% cases. The most common age group with severe thrombocytopenia in the study group was between 50-60 years.

The various mechanisms implicated for thrombocytopenia in malaria is a direct lytic effect of the parasite on the platelet,[12] immune mechanism involving specific platelet-associated IgG antibodies that bind directly to malarial antigen,[13,14] oxidative stress damage due to low levels of platelet superoxide dismutase and glutathione peroxidize activity. Malaria patients usually tolerate low platelet count well due to platelet activation and ability to aggregate. These hyperactive platelets enhance hemostatic response and hence bleeding manifestations are rare in malaria patients despite severe thrombocytopenia[9]

A strong association was noted between thrombocytopenia and the presence of severe malaria. In our study, severe malaria meeting the WHO criteria was noted in 32% of the population accounting to mortality of 7.1%. Similar results were noted in a study by Saravu et al[15]. We considered the presence of renal impairment, hepatic dysfunction and cerebral malaria among the parameters used for the definition of severe malaria.

Renal failure and hyperbilirubinemia were found to be statistically significant with low platelet counts. Severe and profound thrombocytopenia was found to have higher mean creatinine and mean bilirubin levels.

Cerebral malaria was seen in 5% of the study population and was associated with high mortality rates in the current study. Similar results were noted in the study by Saravu et al.[15] The study has established that low platelet count(<50,000/μl), renal failure, hyperbilirubinemia, and cerebral malaria have significant association when death was considered as an outcome with P values<0.05. On multivariate logistic regression analysis of the above parameters, only cerebral malaria had a significant association with mortality with p value=0.023. Our study also noted severe thrombocytopenia (<20,000/μl) was more common in mixed infections whereas recent studies have shown it to be more common with *Plasmodium vivax* malaria.[16]

It was noted that presence of thrombocytopenia in acute febrile illness increases the probability of malaria and low platelet count on first day of admission with acute febrile illness was associated with higher rates of renal failure, jaundice and cerebral malaria with higher mortality rates. Therefore presence of very low platelet count can be used as a harbinger for severe malaria. Its presence should alert the treating physician to keep an eye for the possibility of severe malaria and entails aggressive treatment with intravenous antimalarials. This could be life-saving for patients in resource-limited settings where a battery of tests to establish the diagnosis of severe malaria may not be possible and also the limited supply of intravenous antimalarials could be put to use wisely.

LIMITATIONS:

There was no matched control group with febrile illness and thrombocytopenia. The study duration was short and hence sample size was limited.

CONCLUSION:

It was observed from the study that the presence of thrombocytopenia in a case of acute febrile illness increases the probability of malaria. This finding could be used along with clinical and microscopic parameters to increase the suspicion of malaria and for early treatment initiation. Profound and severe thrombocytopenia was found to have a statistically significant correlation with cerebral malaria, renal failure, and jaundice. Hence the low platelet count on first day of admission with acute febrile illness should alert the treating physician to be more vigilant. Large scale studies are warranted to confirm the above observation.

Acknowledgments:

We thank all the patients and the family who readily agreed to be a part of our study. We would also like to express gratitude to our nursing staff, ancillary personnel and lab technicians for helping us collect the samples on time and process it rapidly.

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