Original Research Article

A STUDY ON RELATIONSHIP OF THROMBOCYTOPENIA AND SEVERE MALARIA IN DAKSHINA KANNADA IN A TERTIARY CARE HOSPITAL

ABSTRACT

Background: Malaria continues to be a huge socio economic burden despite various measures taken to curb the spread worldwide. It is also 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 being thrombocytopenia in malaria.

Aims and objectives

To find the relationship between thrombocytopenia and renal failure, hepatic dysfunction and cerebral 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 population. It was noted that the patients with initial very low platelet count on day 1 were more commonly associated with severe manifestations of 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.

Conclusions

It was noted in our study that 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.Also presence of profound and severe thrombocytopenia was found to have statistically significant correlation with cerebral malaria,renal failure and jaundice.

Keywords: Malaria, Hepatic dysfunction, Renal impairement, 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 4, 35, 000 malaria death worldwide in 2017 according to world Malaria report 2018.[2]The African region accounted for most global cases followed by South East Asian region and 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 risk of malaria and most of whom 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 to 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 in India is 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 sometimes is failed to be recognised. This might result in increased mortality rates secondary to severe malaria. Thrombocytopenia is one of the most commen hematological complications. It increases the likelihood of malaria when present in acute febrile illness by almost 12 to 15 times.[7,8,9]

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 severity of thrombocytopenia with various manifestations of severe malaria to see whether initial platelet count could be used as marker for severe malaria. Also we looked at the relationship between malaria and renal impairment, hepatic dysfunction and cerebral malaria.

MATERIALS AND METHODS

The study included 85 patients admitted in Yenepoya hospital meeting the inclusion criteria. All patients of age >18 years of age and with plasmodium positive species identified by slide positivity and Rapid optimal test [MPFT] getting admitted in Yenepoya Medical College Hospital during the period from December 2016 to June 2018 were included. 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 institutional ethics committee prior to the conduct of the study with protocol number 2016/346 on December 14, 2016. The following investigations were done

Haemoglobin estimation, total WBC count and differential leucocytes count, platelet count, Peripheral smear for malaria parasite, Random blood sugar ,Liver function test and Renal function test – S.urea and S. creatinine. In selected cases arterial blood gas analysis, prothrombin time and activated partial thromboplastin time was 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 parasitaemia:

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 laboured breathing

Hypoglycaemia	Blood or plasma glucose <2.2 mM (<40 mg/dl)
Severe malarial anaemia	A haemoglobin concentration <5 g/dl or a haematocrit 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 oedema	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 parasitaemia >10%

Collected data was analysed 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 significance of various parameters with outcome variables.The level of significance is 5% and analysis was performed using SPSS-17 software.

RESULTS

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

Out of 85 patients in our study 69 were male and 16 were female.All the patients had fever at presentation.The most common clinical presentation was fever noted in 100% of the patients.second most common presentation was headache.None of the patient had convulsions and only 1 patient had bleeding manifestation in the form of petechiae which resolved on its own.The demographic,clinical and lab features of the patient are given in Table 2.

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

In our study 27 patients had severe malaria meeting the WHO severity criteria of which 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 low platelet count of <20,000/µl (When Chi square/Fischer exact test was applied p value was 0.001) . Higher mean bilirubin levels were noted with platelet count <20000/µl and was found to be statistically significant (When Chi square/Fischer exact test was applied p value was 0.001) 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
Age in years-mean	36.68
Men	69(81.2)
Women	16(18.8)
FEVER(%)	85(100)
JAUNDICE(%)	8(9.4)
HEADACHE DYSPNEA(%)	56(65.9) 89(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)

Falciparum(%)	10(11.8)
Vivax(%)	57(67.1)
Mixed(%)	18(21.2)

PATIENT LAB PARAMETERS AND CLINICAL PROFILE	VALUES
Hemoglobin <7 gm % (%)	20(4.7)
7-11gm %(%)	61(23.5)
Leucocyte count <4000 cells/cu mm(%)	20(23.5)
>110000 cells/cumm(%)	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 CHARECTERISTICS IN THOSE WHO DIED AND THOSE WHO SURVIVED

PATIENT CHARACTERISTICS	PATIENT WHO DIED (n=6)	PATIENT 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 mg/dl(mean+SD)	5.88+3.71	1.05+0.42
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 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.

TABLE 4:UNIVARIATE AND MULTIVARIATE ODDS RATIOS OF SELECTED PATIENT CHARECTERISTICS FOR THE OUTCOME DEATH

Patient Charecteristics	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

Our study included 85 patients of malaria from karnataka predominantly from dakshina kannada area.

Complications in severe malaria are either sequestration related 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 seen 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 our study group was between 50-60 years.

The various mechanism implicated in thrombocytopenia in malaria are 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 peroxidise activity.
Malaria patients usually tolerate low platelet count well due to platelet activation and agreeability. These hyperactive platelets enhance hemostatic response and hence bleeding manifestations are rare in malaria patients despite severe thrombocytopenia[9]

Strong association was noted between thrombocytopenia and severity of malaria.In our study severe malaria meeting the WHO criteria was noted in 32% of the population accounting to a mortality of 7.1%.Similar results were noted in study by Saravu et al[15]

Renal failure and hyperbilirubinemia was found to be stastically significant with low platelet counts.In our study 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 study by Saravu et al.[15] It noted in our study that low platelet count(<50,000/µl),renal failure,hyperbilirubinemia and cerebral malaria had significant association with outcome death with P values<0.05.On multivariate logistic regression analysis of the above parameters only cerebral malaria had significant association with mortality with p value=0.023. Our study also noted severe thrombocytopenia (<20,000/µl) was more common in mixed infections where as recent studies have shown it to be more common with Plasmodium vivax malaria.[16]

Hence it was noted that presence of thrombocytopenia in acute febrile illness increases the probability of malaria and low platelet count on day 1 was associated with higher rates of renal failure.jaundice and cerebral malaria with higher mortality rates.Therefore very low platelet count can be used as a harbinger for severe malaria and requires aggressive treatment with intravenous antimalarials.

LIMITATIONS:

There was no matched control group with febrile illness and thrombocytopenia

CONCLUSION:

It was observed from the study that 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 statistically significant correlation with cerebral malaria,renal failure and jaundice. Hence the low platelet count on Day 1 should alert the treating physcian to be more vigilant. Large scale studies are warranted to confirm the above observation.

REFERENCES

1. Centers for Disease Control and Prevention. www.cdc.gov/malaria_worldwide/impact.html
2. World Health Organization.World malaria report;2018 nov.Available from https://www.who.int/malaria/publications/world-malaria-report-2018/en/
3. Kondrashin AV. Malaria in the WHO Southeast Asia region. Indian journal of malariology. 1992 Sep 1;29(3):129-60.
4. Kumar A, Valecha N, Jain T, Dash AP. Burden of malaria in India: retrospective and prospective view. The American journal of tropical medicine and hygiene. 2007 Dec 1;77(6_Suppl):69-78.
5.World Health Organization.World malaria report;2017.Available from https://apps.who.int/iris/bitstream/handle/10665/259492/9789241565523-eng.pdf;sequence=1
6.A Profile of National Institute of Malaria Research. Estimation of True Malaria Burden in India. pp 91-99. Available at http://www.mrcindia.org/MRC_profile/profile2/Estimation of true malaria burden in India.pdf

7. Maina RN, Walsh D, Gaddy C, Hongo G, Waitumbi J, Otieno L, et al. Impact of *Plasmodium falciparum* infection on haematological parameters in children living in Western Kenya. Malar J. 2010;9(suppl 3):S4.
8. Adedapo AD, Falade CO, Kotila RT, Ademowo GO. Age as a risk factor for thrombocytopenia and anaemia in children treated for acute uncomplicated *falciparum* malaria. J Vector Borne Dis. 2007;44:266–71.
9. Lathia TB, Joshi R. Can hematological parameters discriminate malaria from nonmalarious acute febrile illness in the tropics? Indian J Med Sci. 2004;58:239–44.
10. WHO. Tropical Medicine and International Health is published by John Wiley & Sons., 19 (Suppl. 1), 7–131
11. Kochar DK, Das A, Kochar SK, Saxena V, Sirohi P, Garg S,et al. Severe Plasmodium vivax malaria: a report on serial cases from Bikaner in northwestern India. Am J Trop Med Hyg 2009; 80: 194-8
12. Menendez C, Fleming AF, Alonso PL. Malaria-related anaemia. Parasitol Today 2000; 16:469-76
13. Jadhav U, Patkar V, Kadam N. Thrombocytopenia in malaria—correlation with type and severity of malaria. JAPI. 2004;52:615-8.
14. Makkar RP, Mukhopadhyay S, Monga A, Monga A, Gupta AK. *Plasmodium vivax* malaria presenting with severe thrombocytopenia. Braz J Infect Dis. 2002;6:263–5
15. Saravu K, Docherla M, Vasudev A, Shastry BA. Thrombocytopenia in vivax and falciparum malaria: an observational study of 131 patients in Karnataka, India. Annals of Tropical Medicine & Parasitology. 2011;105(8):593-8.
16. Gupta, Narendra Kumar et al. "Study of thrombocytopenia in patients of malaria" *Tropical parasitology* vol. 3,1 (2013): 58-61.