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A study of the thrombocytopenia associated with malaria in the vicinity of Ramganga River in U.P.

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Abstract

Background and objectives: *Plasmodium* transmitted by infected female Anopheles mosquitoes, causing malaria, and anemia is observed; however, we found thrombocytopenia also as an unusual accompaniment in many cases. Platelet count was also evaluated for assessing severity of the infection to correlate it in *P. vivax* and *P. falciparum* cases and to determine the severity of the disease with its level.

Method: The study was conducted in 252 febrile patients seen between August 26th 2018 to September 16th 2018 in the camp organized by the Rajshree Medical Research Institute (RMRI) Bareilly on the bank of Ramganga River. Total Platelet count was analyzed in various species of malaria positive patients. Autopsy were also done in two cases.

Results: In this study, 198 (78.57%) were positive for *Plasmodium vivax*, 40 (15.88%) were positive for *P. falciparum* and 14 (5.55%) had mixed infection. Majority were having thrombocytopenia. Severe thrombocytopenia cases were found in severe state of disease. Signs of bleeding and clotting disorders were seen in autopsy.

Interpretation and conclusion: Thrombocytopenia in patients of acute malaria is not so uncommon, however, platelet count has not been given due attention. This study can have therapeutic implications of avoiding unnecessary platelet infusion in malaria patients with relatively not too lower level of thrombocytopenia.

Keywords: *Plasmodium*, thrombocytopenia, autopsy, bleeding disorders

Introduction

In countries where malaria had been previously eradicated or adequately controlled have recently seen a resurgence of it and it continues to be a cause of high mortality and morbidity in India as well as other parts of the developing world. A clinical diagnosis is widely used in addition to microscopic examination.

Thrombocytopenia has been reported to be associated with *vivax* malaria as well as *falciparum* malaria [1, 2]. It is more common with malaria than with other febrile disease [3]. With about 9.5 million malaria cases in 2017, down 3 million cases since 2016, India is no longer among the top three countries with the highest malaria burden. Among the 11 nations with 70% of the world's burden of malaria, only India has managed to reduce its disease burden, registering a 24% decrease between 2016 and 2017 [4]. However, 1.25 billion Indians (94% of its population) are still at risk of malaria, the report noted.

Globally, the progress made against malaria has stalled for the second consecutive year: The annual report produced by the World Health Organization (WHO) [5] revealed a plateauing. In 2017, there were an estimated 219 million cases of malaria, compared to 217 million the year before. Previously, people contracting malaria globally had been steadily falling, from 239 million in 2010 to 214 million in 2015.

India has set 2030 as the target year for eliminating malaria. It currently accounts for 4% of global malaria cases and 52% of malaria deaths outside the African region. "Government made up its mind that malaria elimination is a cause worth investing in," said Srinivas.[6]In 2017. India launched its five-year National Strategic Plan for Malaria Elimination.[4]The plan is a landmark in India's fight against the disease that shifted focus from malaria "control to elimination". The plan provides a roadmap to end malaria in 571 of India's 678 districts by 2022.With 24% decline in malaria cases, India is on track to reduce malaria cases by 20-40% by 2020, said the World Malaria Report 2018.

Material & Methods

The blood investigations were carried out in the Rajshree Medical Research Institute, Bareilly which itself is situated near the Ramganaga River having a hinterland of Moradabad and Ruhelkhand(Bareilly) divisions of the western U.P.A total 252 patients were included in this study who were found positive for malaria parasite by Malaria antigen test(MP Card Test). Antibodies to detect malaria antigens in the patient's blood. A drop of blood is placed on the test strip where the antibodies and antigen combine to create a distinct line indicating a positive test.

We found that 95.4 per cent of malaria patient had thrombocytopenia and the proportion with malaria increased as platelet count decreased. Thrombocytopenia was defined as platelet count of less than 150000/mm [3]. Platelets count was done by sampling the blood in EDTA vial and whole blood was drawn in automatic analyzer machine (3 part analyzer machine i.e. WBC, RBC and Platelets).

The sensitivity of the malaria antigen was 96.4% and its specificity was 98.9%. Non-malarial or those who were not confirmed on test were excluded. Total platelet count was also done in all cases.

The patients were divided into three subgroups (Grades) based on platelet count:

Grade I. (Mild) - 100000-150000/mm^3
Grade II. (Moderate)- 50000- 100000/mm^3
Grade III. (Severe)- 200000-50000/mm^3
Grade IV. (Very severe)- Less than 20000/mm^3

The speculated mechanisms are coagulation disturbances, sequestration, spleen, antibody mediated platelet destruction, oxidative stress and the role of platelets as co factors in triggering severe malaria. Abnormalities in platelets structure and function have been described as a consequence of malaria and in rare instances platelets can be invaded by malaria parasites[10,11]. We also find out the frequency and the degree of thrombocytopenia in patients with malaria.

Results

In our study, 252 patients with malaria positive were investigated with platelets counts. Out of 252 cases 162 (62.49%) were male and 90 (35.71%) were females [Table-I]. Age groups wise maximum number of patients were in 15 years to 25 years (11.90%) followed by 41 years to 60 years (3.96%) [Table- I].

Table 1: Age and Sex Distribution of Malaria Cases

Age (in years)	Male (%)	Female (%)	Total (%)
1-14	45(17.85%)	27(10.71%)	72(28.57%)
15-25	54(21.42%)	30(11.90%)	84(33.33%))
26-40	3212.69%)	23(9.12%)	55(21.82%)
41-60	31(12.30%)	10(3.96%)	41(16.27%)
Total	162(64.29%)	90(35.71%)	252(100%)

The chi-square statistic is 3.2825. The p-value is.350086. The result is not significant at p <.05.

All patients had previous history of fever (100%) followed by fever with rigor and chills (79.77%), fever with rigor (91.27%), fever with chills (75.40%), nausea (79.44%), vomiting (83.33%), anorexia (71.43%), diarrhea (4.37%), anemia (69.44%), splenomegaly (17.07%), hepatomegaly (3.57%) and jaundice (14.29%) [Table-II].

Table 2: Symptoms and Signs of the Malarial Cases.

Symptoms/Signs	Male (%)	Female (%)	Number of patients	(%)
Fever	162 (64.29%)	90 (35.71%)	252	100%
Fever with rigor and chills	129 (64.18%)	72 (35.82%)	201	79.77%
Fever with rigor	148 (64.35%)	82 (35.65%)	230	91.27%
Fever with chills	124 (65.26%)	66 (34.74%)	190	75.40%
Nausea	110 (62.86%)	65 (37.14%)	175	69.44%
Vomiting	134 (63.81%)	76 (36.19%)	210	83.33%
Anorexia	115 (63.89%)	65 (36.11%)	180	71.43%
Diarrhea	7 (63.64%)	4 (36.36%)	11	4.37%
Anemia	114 (65.14%)	61 (34.86%)	175	69.44%
Splenomegaly	29 (67.44%)	14 (32.56%)	43	17.07%
Hepatomegaly	6 (66.67%)	3 (33.33%)	9	3.57%
Jaundice	23 (63.89%)	13 (36.11%)	36	14.29%

Out of 252 patients, 198 (78.57%) patients were *vivax* positive followed by 40 (15.88%) patients were *falciparum* positive and 14 (5.55%) patients were mixed infection [Table-III].

Table 3: Type of Malaria Parasite Infection

Type	Male (%)	Female (%)	Total Number	Percentage of total number 252
Vivax	145 (73.23%)	53 (26.77%)	198	78.57%
Falciparum	17 (42.5%)	23 (57.5%)	40	15.88%
Mixed	8 (57.14%)	6 (42.46%)	14	5.55%
Total	170	82	252	100%

The chi-square statistic is 15.0367. The *p*-value is.000543. The result is significant at *p* <.05.

80 (31.75%) cases had Grade I thrombocytopenia followed by 101 (40.08%) had Grade II thrombocytopenia, 69 (27.38%) and 05 (1.98%) cases had Grade IV thrombocytopenia. Autopsy done in two cases (both suffering from *falciparum* malaria) shown brain blood vessels were congested and clogged by erythrocyte clusters [Table-IV].

Table 4: Grading of Thrombocytopenia with outcome of Treatment Modality

Grades	Male (%)	Female (%)	Total Number (%)	Treatment modality	Survival	Mortality
Mild	54 (68%)	26 (32%)	80 (100%)	Standard antimalarial drugs	Cured	Nil
Moderate	72 (71.29%)	29 (28.71%)	101 (100%)	Standard antimalarial drugs and Oral hydration	Cured	Nil
Severe	48 (69.57%)	21 (30.43%)	69 (100 %%)	Standard antimalarial drugs and IV Hydration	Cured	Nil
Very severe	4 (75%)	1 (25%)	05 (100%)	Standard antimalarial drugs and Platelet infusion	05	02

The chi-square statistic is 0.5553. The *p*-value is.906574. The result is *not* significant at *p* <.05.

Discussion

Malaria caused by *P. vivax* and *P. falciparum* is endemic in many parts of India. This study found thrombocytopenia, defined as platelet count less than 1, 50000/mm^3 to be a highly sensitive test for malarial severity and it is also frequently associated with hematological complications like bleeding disorders which were also found in autopsy studies. In our study thrombocytopenia was seen in69.44% of cases while the other studies showed 72% [7, 8]. Exact mechanism of thrombocytopenia in malaria cannot be said however

Fajarado and Tallent had suggested a direct lytic effect on the platelets by the malarial parasites demonstrating P. *vivax* within platelets [9]. Immune mechanism [10] as well as non-immunological destruction involving specific platelet associated IgG antibodies binding directly to malarial antigen in the platelets have been updated in the recent past playing a role in the thrombolysis [11]. We also found more significant thrombocytopenia in *P. vivax* malaria like the study of NK Gupta, *et al* [12].

Based on the finding of low levels of platelet superoxide-dismutase and glutathione peroxidase activity and high platelet lipid peroxidation levels in malaria patients, oxidative stress damage of platelets has also been implicated in the etiopathogenesis when compared to those of healthy subjects [13].

As platelet forming megakaryocytes are usually normal or increased. In the marrow decreased thrombopoeisis could not be the cause [13-16]. Low platelet count is well-tolerated in malaria which could be explained by platelet activation and an enhanced agreeability [17] haemostatic responses may be enhanced by the hyperactive platelets and so bleeding episodes are very rare in acute malarial infections, despite significant thrombocytopenia [18]. This we could find in 5 cases (about 2%) in our study which is not so rare and may be due to some errand reasons in this part of the country needing further study.

More cases of thrombocytopenia in *vivax* malaria infection may attribute to possible development of a new genotype of *P. vivax* [18]. Data in India has shown thrombocytopenia exhibited a heightened frequency and severity among patients with *P. vivax* infections [19]. Significant thrombocytopenia was observed in studies from the Indian subcontinent in *P. vivax* malaria [20, 21]. The similar results were from Qatar and Venezuela [22, 23].

Autopsy done in two cases (both suffering from *falciparum* malaria) blood vessels of brain were congested and clogged by erythrocyte clusters. Fine black pigments were found in the erythrocytes and inside the capillary lumen. A study of fatal cerebral malaria in 37 parasitaemic Malawian children [24] compared autopsy evidence of intracerebral parasite sequestration with ante-mortem clinical findings. In seven cases, autopsy revealed an alternative cause of death and no intracerebral sequestration, while in 13, there was intracerebral sequestration and no alternative cause of death. In malaria endemic areas, death due to unexplained fever, jaundice or severe hepato-splenomegaly should be critically investigated and finding of malarial pigments in autopsy examination helps to solve unexplained death in case of fever. Clinically severe jaundice with fever and splenomegaly with slate gray color on autopsy examination raises the suspicion of malaria which can be diagnosed by autopsy examination.

The limitation of the study is no matched control group which was not possible in a severe outbreak of epidemic with limited resources at our disposal.

Higher frequency of mild to severe thrombocytopenia was observed in malaria. Patients with severe thrombocytopenia may be more likely to have *falciparum* malaria than *vivax.* Infusions of platelets were needed only in very severe cases having platelet count less than 20000/m^3 who require prompt initiation of platelet infusion. A normal platelets count in such circumstances may suggest a broader differential diagnosis for the fever. We propose that the platelet count serve as an important initial screening tool in this setting. Platelet infusion in cases having more than 20000/m^3 is not of much therapeutic advantage, however, further study in cases between 20000- 50000/mm^3 warrants study from different parts of the country.

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