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Original Article

Thrombocytopenia with bleeding manifestations in childhood malaria

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ABSTRACT

Background: Thrombocytopenia is frequently found in malaria, but its prognostic value has not been addressed in children. Bleeding with thrombocytopenia in malaria is not so common but can be a cause of mortality if left unattended. **Objective:** To study the occurrence and severity of thrombocytopenia with bleeding manifestations in children with malaria. **Materials and Methods:** This cross-sectional study was conducted in a pediatric hospital of north India. All positive cases of malaria <15 years of age admitted to the hospital between January 2008 and December 2013 were included in the study, and data were recorded on pre-designed pro forma. Patients were further assessed for thrombocytopenia and bleeding manifestations. Data were analyzed by Chi-square test and independent sample *t*-test using SPSS version 16. **Results:** Total 185 cases were included in the study with a median age of presentation of 4 years. *Plasmodium vivax* was identified in 142 (77%) patients, whereas *Plasmodium falciparum* in 31 (17%) and mixed infection in 12 (6%) patients. Thrombocytopenia was observed in 79 (43%) cases, of which 35 (44%) cases had mild, 30 (38%) cases moderate, and 14 (18%) cases had severe thrombocytopenia. Total 10 (5.4%) patients had bleeding manifestations, and all of these had thrombocytopenia. The most common bleeding manifestation was gastrointestinal bleeding presenting as malena. No significant association was found between bleeding and severity of thrombocytopenia (p=0.527) or species of malaria (p=0.682). Furthermore, no significant association was found between severity of malaria and thrombocytopenia (p=0.365). **Conclusion:** Thrombocytopenia and bleeding were not significantly associated with the type of malaria. In an endemic area, if a child presents with acute fever and thrombocytopenia with or without bleeding manifestation, diagnosis of malaria should be strongly suspected.

Key words: *Bleeding, Children, Malaria, Thrombocytopenia*

Malaria is an important tropical disease, affecting 200-300 million patients annually with 650,000 deaths [1]. Presently, about 2 million cases and 1000 deaths due to malaria are reported annually in India accounting for 75-77% of the total malaria cases in Southeast Asia Region [1,2]. Four species of protozoa *Plasmodium* cause malaria in human: *Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae,* and *Plasmodium ovale*. Of these species, *P. vivax* and *P. falciparum* are the most common causative agents. Some cases from Andaman and Nicobar islands were reported to be infected by fifth species *Plasmodium knowlesi* [3]. *P. falciparum* infection is the most serious and responsible for most of the deaths among children in Africa and India [1]. Symptoms in children can differ from those in adults and, as children often have other febrile illnesses; malaria may not be suspected initially [4].

Thrombocytopenia has been reported to be associated with malaria with an incidence ranging from 60% to 80%, with some studies reporting a lower incidence of vivax malaria as compared to falciparum malaria [5]. Good tolerance to low platelet counts is well-known in malaria and significant bleeding is uncommon without associated disseminated intravascular coagulopathy (DIC) [6,7]. In view of paucity of data on bleeding manifestations in Indian children, we have attempted to correlate the low platelet count with bleeding in various types of malaria infections.

MATERIALS AND METHODS

This cross-sectional study was conducted in a pediatric hospital in North India between January 2008 and December 2013. Children aged between 0 and 15 years admitted with the diagnosis of malaria were included in the study. Diagnosis of malaria was made on the basis of thick and thin smear by Giemsa staining showing non-sexual forms of malaria parasite or falciparum and non-falciparum antigen detection by immunochromatographic rapid diagnostic tests (RDTs) or both [8]. Species were identified on the basis of thin smear using Giemsa stain or by RDTs. Children with history and clinical features suggestive of or diagnosed cases of chronic liver disease, idiopathic thrombocytopenic purpura,

bleeding disorders, hematological malignancy, dengue, human immunodeficiency virus (HIV), and sepsis or with intake of hemolytic agents were excluded from the study.

Data about all the recruited patients were collected in a pre-designed pro forma which included demographic profile of the patients, clinical features and examination findings, and relevant investigations such as platelet counts, complete blood count, liver function test, general blood picture, blood culture, ELISA for HIV, NS1, and immunoglobulin M for dengue (in thrombocytopenic patients). Platelet counts were done, on the day of presentation before starting antimalarial drugs, on automated quantitative counters and further checked manually.

Thrombocytopenia was defined as platelet count of <150,000 cells/μL. Patients were divided into three subgroups based on platelet counts. Thrombocytopenia was considered severe if platelet count was <50,000 cells/μL, moderate if between 50,000 and <100,000 cells/μL, and mild if between 100,000 and <150,000 cells/μL [9]. Data were compiled using MS Office Excel and were analyzed by Chi-square test and independent sample *t*-test using SPSS version 16.

RESULTS

Total 208 patients were admitted the diagnosis of malaria during the study period, out of which, 185 met the inclusion criteria and were included in the study. Of these, 132 (71%) were males and 53 (29%) were females. 105 (57%) cases including 70 males and 35 females belonged to 0-4 years age group. 54 (29%) - 38 male and 16 female - were from 5 to 9 years and rest 26 (14%) - 24 male and 2 female - were 10-15 years age group.

The majority of the patients with malaria (57%) as well as thrombocytopenia (26%) were in the age group of 0-4 years (Table 1) with median age of presentation of 4 years. Platelet count ranged from 10,000 to 600,000 cells/μL. The lowest documented count of 10,000/μL was found in a case of *P. vivax* infection. Severe thrombocytopenia was found in 9 (6%) cases of vivax malaria and in 5 (16%) cases of falciparum malaria (Table 1).

It was noted that there was no significant association between severity of thrombocytopenia and type of malaria (p=0.394). Although frequency of occurrence of thrombocytopenia was more in the age group of 0-4 years, it was statistically insignificant (p=0.416). Severe malaria [10] (as defined by the WHO) was found in 34% of the patients and mean platelet count among them was 1.65±1.03 cells/μL, while in non-severe cases, it was 2.014±1.11 cells/μL and association of severity of malaria with thrombocytopenia was insignificant (p=0.365).

About 10 (5.4%) patients had bleeding manifestations. The most common bleeding manifestation was gastrointestinal bleeding presenting as malena. No significant association was found between bleeding and type of malaria (p=0.682) or age of patients (p=0.06) (Table 2). The occurrence of abnormal bleeding with severity of thrombocytopenia was also not correlated (p=0.527). Median platelet count among bleeding children was 110,000 cells/μL. The mean duration of hospital stay was 4.6 days. Platelets were transfused to patients who had either bleeding with low platelet counts or platelet counts <20,000 cells/μL. In rest of the thrombocytopenic patients, platelet counts improved spontaneously with antimalarial treatment. Only one patient, a newborn of 18 days, presented with refusal to feed, loose stools, abdominal pain and fever, and tonic-clonic movements. Within 2 days of hospitalization, he developed pulmonary hemorrhage and died. Rest of the children recovered completely and discharged.

DISCUSSION

Malaria is endemic in many parts of the India. Although our geographical area (Kanpur) comes under the low-risk zone of malaria, in recent few years, the number of malaria cases has increased. Malaria affects almost all blood components and is a true hematological infectious disease. Thrombocytopenia and anemia are the most frequent hematological complications of malaria. In endemic areas, malaria has been reported as the major cause of low platelet count and is a sensitive but non-specific indicator of infection with malaria parasite. Platelet counts of <150,000/μL increase the likelihood of malaria by 12-15 times [11,12].

P. vivax was the common species in our study (77%), though some (6%) of the patients who were included in our study had mixed (*P. falciparum* and *P. vivax*) infections. Faseela et al. found similar results, which were attributed to endemicity for malaria in

Table 1: Platelet counts in different age groups and according to species of malaria

Category	>1.5 lakhs/μl	<1.5-1 lakhs/μl	<1-0.5 lakhs/μl	<0.5 lakhs/μl	Total
Species of malaria					
P. vivax	85 (60)	25 (18)	23 (16)	9 (6)	142 (77)
P. falciparum	15 (48)	7 (23)	4 (13)	5 (16)	31 (17)
Mixed	6 (50)	3 (25)	3 (25)	0	12 (6)
Total	106 (57)	35 (19)	30 (16)	14 (8)	185 (100)
Age group (years)					
0-4	66 (64)	15 (14)	14 (13)	10 (9)	105
5-9	26 (48)	14 (26)	11 (20)	3 (6)	54
10-15	14 (54)	6 (23)	5 (19)	1 (4)	26
Total	106 (57)	35 (19)	30 (16)	14 (8)	185

P. vivax: Plasmodium vivax, P. falciparum: Plasmodium falciparum

Table 2: Distribution of cases having bleeding manifestations

Bleeding	Present	Absent	Total
Species of malaria			
P. vivax	8 (6)	134 (94)	142
P. falciparum	2 (6.5)	29 (93.5)	31
Mixed	0	12 (100)	12
Total	10 (5.4)	175 (94.6)	185 (100)
Age groups (years)			
0-4	9 (9)	96 (91)	105 (100)
5-9	0	54 (100)	54 (100)
10-15	1 (4)	25 (96)	26 (100)
Total	10 (5.4)	175 (94.6)	185 (100)
Platelet counts (lakhs/µl)			
<1.5-1	0 (0)	35 (100)	35 (100)
<1-0.5	3 (10)	27 (90)	30 (100)
<0.5	7 (50)	7 (50)	14 (100)
Total	10	69	79

P. vivax: Plasmodium vivax, P. falciparum: Plasmodium falciparum

central India [13]. In our study, thrombocytopenia was noticed in 73 (43%) of the cases which was more common with age group of 0-4 years and risk of thrombocytopenia subsequently decreased with advancing age. Tanwar et al. found that thrombocytopenia was highest among the age group of 0-5 years with mono-infection and subsequently decreased with advancing age, whereas in *P. falciparum* mono-infection. It was reverse [14].

In our study, the prevalence of thrombocytopenia was 40%, 52%, and 50% in *P. vivax*, *P. falciparum,* and mixed infection, respectively. Mild to moderate thrombocytopenia was more common than severe thrombocytopenia. Maina et al. and Lathia and Joshi also reported thrombocytopenia in 40% and 59% of children with malaria, respectively [11,12]. Rodriguez et al. had reported the similar prevalence of thrombocytopenia in vivax and falciparum malaria [15]. Some studies reported a higher incidence of thrombocytopenia in this age group [16-18]. A study from Northwestern India stated significant association of thrombocytopenia and vivax malaria [19].

Severe thrombocytopenia is commonly reported to be associated with *P. falciparum* infection and has been reported in co-infection with both *P. falciparum* and *P. vivax* while it is rarely reported in *P. vivax* malaria [20]. In our study, severe thrombocytopenia was found more commonly (16%) with *P. falciparum* than with *P. vivax* (6%) cases; however, the prevalence of mild and moderate thrombocytopenia was equal. We did not find a significant association between severity of thrombocytopenia and species of malaria. A study from Central India reported higher prevalence (38%) of severe thrombocytopenia with vivax malaria [9]. Another Indian study found platelet count <20,000/µL in 1.5% cases of vivax malaria as against 8.5% cases of falciparum malaria [21]. In our study, platelet count <20,000/µL was noticed in 2.2% of cases (2.8% and 3.2% with vivax and falciparum infection, respectively). In our study, the least platelet count (10,000 cells/µL) was associated with vivax infection which is consistent with other Indian studies [9,22,23].

In our study, all the children having bleeding manifestations had thrombocytopenia, but low platelet counts were not always associated with abnormal bleeding. It suggests that some unknown factors played role in bleeding in malaria and not only the low platelets or species of malaria. The exact mechanism of thrombocytopenia is not well understood; however, immune-mediated lysis and sequestration in the spleen have been documented. An abnormality in platelet structure and function has been described as a consequence of malaria parasites invasion. Decreased thrombopoiesis is not a contributing factor as platelet-forming megakaryocytes in the marrow are usually normal or increased [11,24,25].

Thrombocytopenia seen in complicated falciparum malaria is due to DIC along with platelet endothelial activation, but the one seen in uncomplicated malaria-like *P. vivax* has multifactorial etiology. A few postulated mechanisms are macrophage activation leading to platelet destruction [26], increased levels of cytokines [27], immunological destruction due to antiplatelet immunoglobulin G [28], oxidative stress [29], and shortened platelet life span in peripheral blood and sequestration in non-splenic areas [30] and partly due to pseudothrombocytopenia due to clumping of platelets [31]. Two types of changes in platelet dysfunction are seen in malaria. Initially, there is platelet hyperactivity this is followed by platelet hypoactivity. Platelet hyperactivity results from various aggregating agents such as immune complexes, surface contact of platelet membrane to malarial red cells, and damaged endothelial cells. This can activate the coagulation cascade and contributes to DIC. Transient platelet hypoactivity is seen following this phase and returns to normal in 1-2 weeks [32,33].

A good tolerance of low platelet counts is well known in malaria this could be explained by platelet activation and an enhanced aggregability [6]. Clinical bleeding in severe malaria is not a common feature and occurs in <5-10% of individuals with severe disease. In most of the studies, including ours, thrombocytopenia has not been associated with significant mortality in malaria. It usually disappears with the treatment of the disease and requires no treatment for itself; although, we gave platelet transfusions to the patients who had platelet count <20 000 cells/µL or patients with thrombocytopenia and bleeding.

There are certain limitations of our study. First, this was a hospital-based study conducted in a low malaria zone; so, this study may not represent the accurate burden of malaria and thrombocytopenia related to malaria. Second, we did not correlate the baseline thrombocytopenia with post-treatment thrombocytopenia, which could have been useful in this context. However, there are no reports of quinine-induced thrombocytopenia in malaria [22].

CONCLUSION

The presence of thrombocytopenia is not a distinguishing feature between the two types of malaria and platelets <20,000/µL can be found in *P. vivax* malaria also. Bleeding manifestations, though

uncommon, may occur in children with malaria irrespective of species of malaria or severity of thrombocytopenia.

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