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Severity of Thrombocytopenia and Prolonged Bleeding Time in Patients with Malaria (A Clinical Study of 162 Malaria Cases)

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Abstract: To evaluate the severity of thrombocytopenia and prolonged bleeding time in patients with malaria. This cross sectional descriptive study was conducted at tertiary care hospital. All patients above 12 years of age, of either gender present with shaking chills, high grade fever, sweating and are often associated with fatigue, headache, dizziness, nausea, vomiting, abdominal cramps, dry cough, muscle or joint pain, back ache or fever with unconsciousness and febrile seizers were enrolled and evaluated for presence of malaria through thick and thin blood smear slides. The malaria diagnosed subjects were further assessed for thrombocytopenia and its severity. Out of 182 suspected cases of malaria, 162(89%) were found to be positive for malarial parasite on blood smear slides with mean age 39.31 ± 7.63 (SD).The *Plasmodium vivax* was identified in 85(52%) patients while *Plasmodium falciparum* was in 77(48%) subjects. The females were seventy seven (48%) where as remaining 52% were males (P=0.04). The thrombocytopenia was observed in 117 (72%) subjects, of which 30 had mild (26%), 58 (49%) had moderate and 29 (25%) had severe thrombocytopenia (P=0.01). Out of one hundred sixty two, 60(37%) patients were unconscious, 12 (7%) were semiconscious and 90 (56%) patients were conscious. In 32 *Plasmodium vivax* infected and 42 *Plasmodium falciparum* infected thrombocytopenic patients the bleeding time was observed as prolonged. The thrombocytopenia and prolonged bleeding time was identified in *Plasmodium vivax* and *Plasmodium falciparum* malaria.

Key words: Thrombocytopenia · Malaria · *Plasmodium vivax* · *Plasmodium falciparum* · Bleeding time

INTRODUCTION

Malaria is estimated to be directly responsible for around one million deaths annually worldwide [1]. The morbidity and mortality burden caused by malaria is nearly 3% [2]. Even though Africa accounts for 90% of the mortality burden for malaria, South-east Asia still suffers considerable mortality and morbidity. Malaria is a major public health problem in Bangladesh and 10 out of its 64 districts (around 17.9 million people) are thought to be highly endemic (>1 case per year per 1,000 population) malaria with highly seasonal transmission. All of these districts are in the east and southeast of the country near to the borders with India and Myanmar [3]. *Plasmodium vivax* causes up to 65% of malaria in India and is becoming increasingly resistant to malaria drugs. By contrast, *Plasmodium falciparum* is the most deadly species and the subject of most malaria-related research and literature [4]. *Plasmodium falciparum* is the most common cause of severe (life-threatening) malaria. It affects all age groups, although the reported mortality varies considerably depending upon the age, immunity, clinical complications and access to appropriate treatment [5]. The mortality is higher in adults with severe falciparum malaria than in children with similar disease as evidenced by the fact that mortality amongst South East Asian adults with renal failure due to severe malaria is 45% while the mortality amongst Kenyan children with severe anaemia is only 1% [6-8]. Intensive care with facilities for ventilation and haemodialysis appears to reduce the mortality [9-10]. The reported prevalence of malaria in Pakistan is 43% [11]. Malaria can cause hemostatic abnormalities that range from asymptomatic thrombocytopenia to fulminant disseminated intravascular

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coagulation (DIC) [12]. Early investigators suggested that the major coagulation abnormality of malaria was DIC, but in recent years clinicians have recognized that thrombocytopenia is a common and early sign of malaria infections, whereas DIC is rare [13]. It has been estimated that "80% of patients infected with either *P. vivax* or *P. falciparum* malaria develop thrombocytopenia during their infection and although the thrombocytopenia is caused by increased platelet destruction, the mechanism has been unknown [14].

There is no extensive local literature is available on such topic, therefore by keeping and considering such debate in mind the present study was conducted at a tertiary care teaching hospital that covers both rural as well as urban population and provide all health related emergency facilities. The present study evaluates the haematological disturbance in patients with malaria in relation to thrombocytopenia, bleeding time and also provides local epidemiological data of malaria infected subjects as far as thrombocytopenia and bleeding time is concerned.

MATERIALS AND METHODS

This cross sectional descriptive study was conducted in the department of medicine at Liaquat University Hospital Hyderabad, Sindh, Pakistan from October 2003 to August 2005. All patients above 12 years of age, of either gender present with shaking chills, high fever and sweating, associated with fatigue, headache, dizziness, nausea, vomiting, abdominal cramps, dry cough, muscle or joint pain, back ache or fever with unconsciousness and febrile seizers came through outdoor patient department (OPD), indoor patient and causality outdoor department (COD) were evaluated and enrolled in the study. The referred suspicious patients of malaria referred from different departments were also included in our study. The technique used for sample collection was non probability purposive. The data was collected through a pre-formed proforma / questionnaire. The detail history of all such patients was taken; complete clinical and relevant examination was performed. For the evaluation of malaria all such subjects were screened for malarial parasite by taking 4cc venous blood sample in a disposable syringe, transfer it in a specific (CP) bottle and then sent to laboratory for analysis through thick and thin blood smear slides. The immunochromatographic tests was also performed (whenever need). The exclusion criteria were; (i) The patients with meningitis, encephalitis, pharyngitis and urinary tract infections. (ii) The non cooperative patients or who refused to participate in the study. All malaria diagnosed subjects were assessed for platelet count through complete blood picture and thrombocytopenia (if present) was classified according to the protocol used by Memon *et al.* [15] i.e. mild (<150,000 to >50,000/l.), moderate (<50,000 to >20,000/l.) and severe (<20,000/l). The malaria infected thrombocytopenic patients were further evaluated for their bleeding time (BT) by Duke method i.e. the patient is pricked with a special needle or lancet, preferably on the earlobe or fingertip, after having been swabbed with sprit. The prick is about 3-4 mm deep and the patient then wipes the blood every 30 seconds with a filter paper. When bleeding ceases it was labeled as normal or prolonged according to the cut off range (the normal bleeding time is 4-8 minutes and it was considered as prolonged when it is > 8 minutes). The informed consent was taken from every patient or from attendant of patients after full explanation of procedure regarding the study and all such maneuvers were under medical ethics. The data was collected, saved and analyzed in SPSS version 10.00. The frequency and percentage of thrombocytopenia was calculated by assessing the platelet level. The frequency and percentage was also calculated for gender distribution. The mean and standard deviation was calculated for age. The chi-square test was applied between categorical variables and the p-value ≤ 0.05 was considered as statistically significant.

RESULTS

Out of 182 suspected cases of malaria, 162(89%) were found to be positive for malarial parasite on blood smear slides with mean age 39.31 ± 7.63 (SD). The *Plasmodium vivax* was identified in 85 (52%) subjects while *Plasmodium falciparum* was observed in 77 (48%) subjects. The gender distribution is mentioned in Table 1. The thrombocytopenia was observed in 117 (72%) and its severity is shown in Table 2. Of one hundred sixty two 73 (45%) patients presented through causality outpatient department (COD), 78(48%) through outpatient department (OPD) and 11 (7%) were referred from different wards i.e. Gynaecology & Obstetrics and Surgery where they were initially admitted but during hospitalization they were developed fever and non specific symptoms and after evidentially diagnosed as malaria were referred to medical department for specific management. The identified features were malaise 121 (75%), fatigue 133(82%), headache in 148 (91%) and heavy menstrual bleeding in 9(6%) patients. Out of one hundred

Table 1: Gender Distribution of Patients with Malaria

	Gender (n = 162)		
Specie	Male	Female	P-Value
Plasmodium vivax	51 (60%)	34 (40%)	0.04*
Plasmodium falciparum	34 (44%)	43 (56%)	
Total	85(60%)	77(40%)	

*p-value is statistically significant
Chi-square value = 4.067, df = 1

Table 2: Thrombocytopenia in Patients with *Plasmodium vivax* and Falciparum Malaria

	Thrombocytopenia (n =117)			
Specie	Mild	Moderate	Severe	P-value
Plasmodium vivax	24 (35%)	27 (39%)	18 (26%)	0.01*
Plasmodium falciparum	06 (13%)	31 (65%)	11 (23%)	
Total	30 (26%)	58 (49%)	29 (25%)	

*P = statistically significant
Chi square value = 9.296, df = 2

sixty two, 60(37%) patients were unconscious, 12(7%) were semiconscious and 90(56%) patients were conscious. Four patients were expired 4(2%), 23(14%) patients left ward against the medical advice, 17(10%) patients left the ward on request (discharge on request) while 118 (73%) patients were recovered and discharged from hospital. Ninety eight (60%) patients were belonged to rural areas while remaining 64(40%) were belonged to urban areas. In 32 *Plasmodium vivax* infected and 42 *Plasmodium falciparum* infected thrombocytopenic patients the bleeding time was observed as prolonged.

DISCUSSION

Acute malaria is often associated with mild or moderate thrombocytopenia in non-immune adults and in children from malaria-endemic areas and is a sensitive but non-specific indicator of infection with malaria parasites. In malaria profound thrombocytopenia is associated with hemorrhagic manifestations or a component of disseminated intravascular coagulation [16-18]. Moreover; thrombocytopenia is associated with the severity of disease or death in malaria. In our study the thrombocytopenia was observed in 72% subjects, however it is consistent with the study by Casals-Pascual *et al.* [19] and Kelton *et al.* [20] The prevalence of thrombocytopenia in malaria was reported as 85% (falciparum) and 72% (vivax) in the study by Horstmann *et al.* published in 2005 [21]. Falciparum malaria presents with protean manifestations and is associated with a variety of complications and has a high mortality.

Thrombocytopenia is a common feature of acute malaria and occurs in both P. falciparum and P. vivax infections regardless of the severity of infection. The absence of the normal quantity of platelets on a peripheral smear in a case of fever is often a clue to the presence of malaria as we had identified in our study as well. Thrombocytopenia is rarely accompanied by clinical bleeding or biochemical evidence of DIC and after recovery the platelet counts rises rapidly. Profound thrombocytopenia with platelet count as low as 5000/il has been reported in the Indian literature, [13] However in our study 26% subjects in P. vivax and 23% subjects in P. falciparum had platelet count <20,000 i.e. severe thrmbocytopenia without any clinically evidence of bleeding. A study conducted in Saudi Arabia on malaria shown anemia in 60% and thrombocytopenia in 53% cases [22].

The exact mechanism of thrombocytopenia is not fully understood however immune mediated lysis, sequestration in the spleen and a dyspoietic process in the marrow with diminished platelet production have been documented. An abnormality in platelet structure and function have been described as a consequence of malaria and in rare instances platelets can be invaded by malarial parasites themselves, where as a study published in 2006 shown that production of IL-10 in acute malaria is responsible for thrombocytopenia. [19] In clinical trials, recombinant macrophage colony stimulating factor (M-CSF) has been known to cause a reversible dose dependent thrombocytopenia. Elevated M-CSF levels in malaria, by increasing macrophage activity may mediate platelet destruction in such cases. Oxidative stress damage of thrombocytes has also been implicated in the etiopathogenesis based on the finding of low levels of platelet superoxide-dismutase and glutathioneperoxidase activity and high platelet lipid peroxidation levels in malaria patients, when compared to those of healthy subject [23]. The prolonged bleeding time in malaria infected thrombocytopenic patients was also observed by Kochar *et al.* [24].

Detection of malarial parasites in peripheral smear is the gold standard for diagnosis of malaria. It is time-consuming and needs expertise, especially to detect the parasite at low levels of parasitemia. Finally we can argue that patient with fever and recent travel history (especially in malaria endemic areas) platelet count may be an important clue to the diagnosis of malaria. Thrombocytopenia should increase the suspicion of malaria and multiple peripheral smears, or a more sensitive test like detection of parasite-specific antigen levels

should be performed. The present study discuss the thrombocytopenia in the light of malaria, therefore in future related studies should be conducted at different public health care settings by focusing the thrombocytopenia in more advance and extensive level.

CONCLUSION

In our study we identified mild to severe thrombocytopenia and prolonged bleeding time in patients with *Plasmodium vivax* and falciparum malaria. Therefore, multicentre studies are needed and carried out over a longer time span to establish the definitive qualitative and quantitative cause and relationship between malaria and thrombocytopenia.

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