

Research Article

Alteration of coagulation profile in malaria patients and its correlation with degree of parasitemia: a prospective study

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ABSTRACT

Background: Malaria is a major health problem in many parts of India. Several factors have been attributed to increased morbidity and mortality in malaria with altered haematological and coagulation parameters playing an important role. This study was performed to find the correlation between the alteration of coagulation profile and degree of parasitemia.

Methods: Fifty patients with Malaria confirmed by PS, or Antigen assay underwent detailed clinical history, thorough physical examination and investigated with routine investigations, haematological and coagulation parameters were recruited in the study.

Results: Parasitemia was found out for each of the patients and were categorized into mild moderate and severe parasitemia. This was followed by monitoring the alteration of coagulation profile with respect to severity of parasitemia. 17 patients had increased prothrombin time and most of these patients were *Plasmodium falciparum* positive. Thrombocytopenia was observed in 58% of the patients. Increased PT has positive co-efficient of correlation to degree of parasitemia with an 'r' value of 0.65 which is significant.

Conclusions: It was found that the number of patients with increased prothrombin time increased with increase in degree of parasitemia, that is, the number of patients with deranged PT in severe parasitemia was significantly more than those in moderate parasitemia and this in turn was more than those in mild parasitemia.

Keywords: Malaria, *Plasmodium falciparum*, Prothrombin Time, Parasitemia, Thrombocytopenia

INTRODUCTION

Malaria is a protozoan disease transmitted by the bite of infected *Anopheles* mosquito. Despite enormous control efforts, increase in the drug resistance of the parasite, the insecticide resistance of its vectors, human travel and migration have contributed to its resurgence and is a leading cause of mortality and morbidity in developing

areas of the world.¹ It is endemic in at least 87 countries, placing approximately 2.5 billion people at risk.^{2,3}

In India 60 to 65% of the infections are due to *Plasmodium vivax* and 35% due to *Plasmodium falciparum*.⁴ In South-east Asia region, India alone contributes 80% of malaria cases.^{5,6} Although there has been a substantial development in treatment and prevention, malaria is a major public health problem in

tropical developing world. *Plasmodium falciparum* infection is often associated with a procoagulant tonus characterized by thrombocytopenia and activation of the coagulation cascade and fibrinolytic system; however, bleeding and hemorrhage are uncommon events, suggesting that a compensated state of blood coagulation activation occurs in malaria.⁷

Common clinical presentation of infection of severe malaria are severe anemia, acidosis, jaundice, acute renal failure, acute respiratory distress syndrome, hyperparasitemia, shock, hypoglycemia, disseminated intravascular coagulation, convulsions, hemoglobinuria, impaired consciousness and extreme weakness.⁸ These occur mostly with *Plasmodium falciparum* malaria.

Malaria should be considered in the differential diagnosis of anyone who presents with a febrile illness and multi organ failure. In many endemic areas malaria is over diagnosed on clinical grounds and it is necessary to make a definite diagnosis wherever possible. However the unambiguous diagnosis of malaria is difficult as examination of peripheral smear is very subjective.

Peripheral smear is a very good diagnostic test if done in the hands of a well-trained individual. The newer antigen tests are more objective and can even detect malaria antigen in those whose peripheral smear is negative because of prior anti-malarial treatment.⁹

Activation of coagulation cascade occurs even in uncomplicated malaria but this is mild and reverts to normal as patients become afebrile and aparasitemic.³² There is accelerated coagulation cascade activity with accelerated fibrinogen turnover, consumption of anti-thrombin 3, reduced factor 13 and increased concentration of fibrin degradation products in acute malaria.¹¹ Coagulation cascade is activated via intrinsic pathway.¹⁰ In severe infection PT and PTT may be prolonged and in few patients (<5%) bleeding may be significant. Intravascular thrombus formation is observed rarely at autopsy in fatal cases. Fibrin deposition is sparse and platelets are strikingly unusual.¹²

Numerous studies with human and animals indicate that there is undoubtedly increased coagulation activity in malaria. It occurs in uncomplicated (mild) cases and, although clinically not significant, can be confirmed as a compensated state according to in vivo coagulation tests.

Activation of coagulation cascade as a consequence of inflammation is an essential part of the host defense of the body. Thus, in uncomplicated malaria, a coagulation disorder is a common laboratory finding, but bleeding and hemorrhage are not observed. Coagulation disorder is also commonly observed in severe malaria (~ 1% of all cases), but only in 5% to 10% of these cases it is associated with bleeding.

Sharma et al reported that incidence of disseminated intravascular coagulation as 16.7% in their series and out of them only 3.3% had bleeding manifestations.¹³ In a study conducted by Butler T et al, out of 53 patients of acute falciparum malaria no one had classical disseminated intravascular coagulation with bleeding. Abnormal coagulation tests sporadically observed were not accompanied by abnormalities with other tests that would establish disseminated intravascular coagulation.¹⁴

In the present we attempted to observe the incidence of alteration in of coagulation profile parameters in malaria infection and correlated with the parasitic index.

METHODS

The present study was conducted at Vydehi Institute of Medical Sciences and Research center, Bangalore, India. The study was carried out on 50 patients admitted in our hospital. A detailed history was taken followed by a detailed clinical examination to assess clinical severity and complications. All the patients in this study were proved to be cases of malaria either by peripheral smear examination (both thick and thin smear) or by malarial antigen assay. Haematological and coagulation parameters like haemoglobin estimation by cyanmethemoglobin method, RBC count by total and differential counts - using Neaberg's chamber, total platelet count by modified DacieLeurs method, prothrombintime, activated partial thromboplastin time ESR estimation by westergren method bone marrow aspiration was considered in patients with pancytopenia and packed cell volume by wintrobe method.

Patients with chronic liver diseases, fever of any other cause, febrile thrombocytopenia of other causes were excluded. Biochemical investigations such as fasting blood sugar, blood urea, serum creatinine, liver function tests and chest X-ray PA view were performed.

All the investigations except bone marrow examinations were done before the treatment was started. Once the patient was diagnosed to have malaria they were started on anti-malarial drugs according to the new WHO guidelines for treatment of malaria. Other supportive treatment was given according to the patients conditions. The data were expressed as mean±SD. Results were analyzed statistically using standard statistical software package of social science (SPSS) version 20. All the groups were compared with the control group. Pearson's correlation analysis was performed on all samples collected from the patients. The difference was considered significant if $p < 0.05$.

RESULTS

In this study the predominant age group affected was between 20-30 years. More than 70% of the patients were young individuals. The number of males affected in our study was more compared to the number of females. In

this study the majority of the population was from rural areas (68%). Fever was present in 96% of the total patients. Chills and rigors were present in 80% of patients with falciparum malaria. It was also seen in 76.67% of patients with vivax malaria. Fatiguability was observed in 46% of the total cases. 46.67% of the patients with falciparum had easy fatiguability and 46.67% of the patients with vivax malaria had fatiguability. Nausea and vomiting was one of the frequent symptom a. The symptom was observed in 26.67% and 23.33% of patients with falciparum and vivax respectively.

Abdomen pain is noted in 13.3% of patients with vivax malaria and with 6.67% of patients with falciparum malaria. Cough is seen in 6.67% of the patients with falciparum and 6.67% vivax respectively. Altered sensorium is noted in 6.67% of the patients with vivax malaria. It was seen in 13.33% of the patients with falciparum infection. Bleeding tendency history was noted only in the patients with mixed infection and falciparum, with none in vivax malaria. Fever was the most frequent symptom followed by chills and rigor being the next most common easy fatiguability was seen in nearly half of the patients.

Pallor was noted in 76% of the total cases. In patients with falciparum it was seen in 93.33% of the patients. Among the vivax malaria it was present in 66.67% of patients and it was seen in 80% of the patients with mixed infection. Anemia was the most frequent physical sign in our study. Icterus was noted in 26% of the total patients. Out of 50 patients in the study 17 patients had splenomegaly. About 33.33% of fthe patients with falciparum malaria had splenomegaly. Incidence of splenomegaly was 23.37% and 100% with vivax malaria and mixed infection respectively.

Pedal oedema was noticed in 12% of the patients. It was noticed among falciparum and mixed infection. It was seen in 3 patients with vivax malaria. It was seen in 6.67%, 10% and 40% of the patients with falciparum, vivax and mixed infection patients.

CNS Involvement in the form of coma and seizures was seen in 14% of the patients. It was not seen in any patient with vivax malaria. It was seen in 7 patients with falciparum infections that is 46.67%.

Plasmodium vivax was the most frequently observed species. It was seen in more than half the cases i.e. 60%. Next common was Plasmodium vivax seen in 30% of cases. Mixed infection consisting of both Plasmodium vivax and falciparum was observed in 10% cases.

30 patients had Hb% less than 10gm /dl. Among the patients who had less than 10gm /dlHb, 15 patients were *Plasmodium vivax*, 11 patients *Plasmodium vivax* and 4 of them had mixed infection.

Anemia was present in 60% of patients and among them 19 had splenomegaly, that is 63.33% of patients with anemia had splenomegaly. Splenomegaly was found to be present in 24 patients out of these 19 were found to be anemic that is 79.17% of patients with splenomegaly had anemia. 29 patients had thrombocytopenia and 75.86% of these had splenomegaly, 24 patients had splenomegaly and 91.67% of these had thrombocytopenia.

In our study thrombocytopenia was observed in 58% of the patients. Out of the 29 patients only 4 patients had severe thrombocytopenia less than 50,000/cmm. 73.3% of the patients with falciparum malaria had thrombocytopenia.

Prothrombin time

Mean PT was 12.782 seconds. It was increased in 34% of the total cases. The increase was noted in 73.3% of the patients with falciparum malaria. It was increased in 10% of patients with vivax malaria and 60% of the patients with mixed infection. But the bleeding tendencies were noted only in 2 patients i.e. 4% of the total cases.

Activated partial thromboplastin time

Mean APTT was 28.91. It was increased in 12% of the total cases. It was found to be increased in 20% of patients with falciparum malaria. 6.67% of the vivax malaria patients had elevated APTT and 20% of the mixed infection patients had elevated APTT. 0.002% - 0.199% being considered mild parasitemia, has 14 patients in this group but the incidence of deranged PT is only 7.14%. 0.2%-1.99% being considered moderate parasitemia has an incidence of 23 in this group with deranged PT in 17.39% of the cases. 2% - 4.99% is considered severe parasitemia and the incidence in this group being 13 patients out of 92.3% have a deranged PT. This shows that with increasing parasitemia the chances of alteration in PT increase. It has also been noted that with increasing parasitemia the derangement in PT also increases. Increased PT has positive co-efficient of correlation to degree of parasitemia with an 'r' value of 0.65 which is significant.

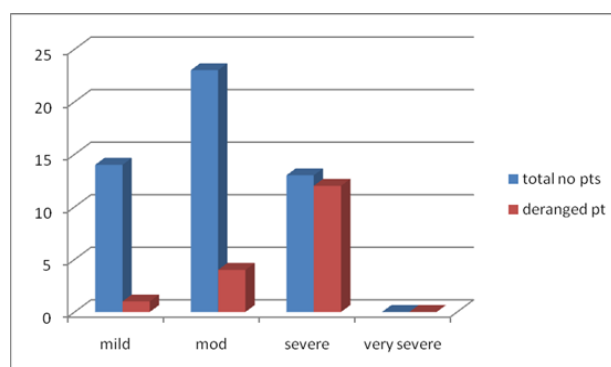


Figure 1: Incidence of derangement of prothrombin time with respect to severity of parasitemia.

DISCUSSION

Activation of the coagulation cascade as a consequence of inflammation is a well known event and can be viewed as an essential part of the host defense of the body, for example, to infectious agents. While activation of the coagulation cascade is a physiologic response triggered in an effort to contain the invading entity and to keep the consequent inflammatory response to a limited area, an exaggerated or uncontrolled response may lead to a situation in which coagulation and microthrombosis contribute to disease. This is illustrated by the occurrence of systemic coagulation activation in combination with microvascular failure, which results from the systemic inflammatory response to severe infection or sepsis and contributes to multiple organ dysfunction.

The concept emphasizing the role of the coagulation cascade in regulating or driving inflammation. It is remarkable that these two situations appear to occur in malaria.⁷

In our study the male to female ratio was 3.17:1 and compared to Bhakshiet al the males affected were more in our study. The incidence of malaria was more in men than in women due to the working pattern i.e men are exposed to mosquito bites outdoors whereas females are less exposed.¹⁵

The working group is the age group which is predominantly affected, because this is the group which is exposed to the mosquito bites especially in the fields and outdoors.

Also our study follows the age pyramid. In a study by Malhotra et al the percentage of people above fifty years was just 4% and also shows the percentage of people affected over 60 years was 4%.¹⁶

The mean age was more than the study done by Sharma et al and Bhakshi et al.^{13,15} In the present study the percentage of vivax malaria was 60% and the incidence of falciparum and mixed infection was 30% and 10% respectively. In a study by Rajansthein et al the prevalence of falciparum was 76.2% whereas vivax malaria was just 23.8%.¹⁷ In a study by Reddy et al there was high incidence of vivax malaria i.e. 61.2% and falciparum being 36.8%.¹⁸ In another study conducted by Bhakshi et al the incidence of falciparum, vivax and mixed infection was 60%, 35% and 5%.¹⁵ The study by Reddy et al was similar to our study.¹⁸ From these observations we can conclude that the incidence of particular species varies with geographical area, the area where we have conducted the study is known to be endemic for vivax and hence the higher incidence in our study.

Anemia was present in 63% of patients in our study the incidence of severe anemia (Hb<6 gm%) was seen in 17% of the patients and it was comparable to study done

by Mehta et al which had severe anemia incidence of 18%.¹⁹ The overall incidence of anemia was higher in studies conducted by Sharma et al where the incidence was 86.7%.¹³

Thrombocytopenia

Thrombocytopenia was present in 58% of the cases in the present study. In a study by Horstmann et al the incidence of thrombocytopenia was 85%.²⁰ Sharma SK et al observed that 70% of the patients had thrombocytopenia.¹³ Kueh et al had observed that 85% of the patients with falciparum malaria had thrombocytopenia.²¹

Prothrombin time was increased in 34% of the total cases and it was increased in 73.3 % of in cases with falciparum malaria. It was increased in 10% and 60% of the patients with vivax and mixed infection. In a study conducted by Royet S al PT was increased in 11.6% of cases.²² In a study of severe falciparum malaria cases by Clemenset R al PT was prolonged in 22.7% of the cases this was similar to the observations in our study.¹⁰

In our study APTT was found to be increased in 12% of the patients. It was increased in 10% of the cases with falciparum malaria and 13.3% of cases with vivax malaria and 20% with mixed infection. In a study conducted by Roy S et al APTT was increased in 16.6% of the patients this was similar to what we observed in our study.²²

In this study it was observed that the number of patients who fell in the severe parasitemia group had a higher incidence of alteration of coagulation profile more so with respect to prothrombin time. The degree of derangement in the severe parasitemia category was also more compared to the mild and moderate parasitemia group.

The incidence of deranged PT was 7.14% in the mild category, 17.39% in the moderate category and 92.3% in the severe category proving that there is definitely an association between degree of parasitemia and derangement of PT.

CONCLUSION

The higher incidence of falciparum in this study is due to the fact that ours is a tertiary centre and is endemic for falciparum malaria. PT and APTT were prolonged in majority of cases, predominantly in falciparum and mixed infections, but this does not result in spontaneous bleeding. Severe anemia is poor prognostic factor and it increased the duration of hospital stay and even mortality. Severity of parasitemia was noted for each of the positive cases and it was found that with increasing severity of parasitemia the number of patients as well as the degree of derangement of the coagulation profile both increased. It was found that the number of patients with increased

prothrombin time increased with increase in degree of parasitemia, that is, the number of patients with deranged PT in severe parasitemia was significantly more than those in moderate parasitemia and this in turn was more than those in mild parasitemia.

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