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COAGULATION PROFILE IN SEVERE FALCIPARUM MALARIA AND ITS CLINICAL CORRELATION

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ABSTRACT

The objective of this study is to evaluate the coagulation disorders in patients with falciparum malaria and to establish a probable pathogenesis. A total 91 adult falciparum malaria patients were selected which got confirmed by peripheral smear examination/ QBC. The complicated malaria accounted for 43%. Complete blood count and coagulation profile (platlet count, PT, aPTT, BT, CT) were done immediately on admission & repeated after 6-8 hrs. Repeat platelet counts were done in subjects with marked thrombocytopenia until normal or near normal values were reached. Thrombocytopenia was found in 73.6% (n=67) of patients, but only 8.79% (n=8) cases presented with bleeding manifestations. In 6.59% (n=6) of cases, the PT, aPTT, FDP was found to be prolonged which belonged to the cases with bleeding manifestations. Hematological changes were mild in the first 24 hours, but continued to deteriorate for few days after anti-malarial therapy. P. falciparum infection was associated with severe hematologic abnormalities, disseminated intravascular coagulopathy. So regular follow up of blood cells and platelets are of utmost importance particularly in cases infected with *P. falciparum* infections.

KEYWORDS: Falciparum, Malaria, Thrombocytopenia

INTRODUCTION

Malaria remained the major health problems worldwide with increased morbidity and mortality. The global case fatality rate of falciparum infection is around 2 million deaths per year [4,10]. There have been great changes in the clinical manifestation of severe malaria in India over the past one decade. Serial works by kochar[8] and his group has shown that there is a major shift in the clinical presentation of Pf malaria from cerebral malaria to fever with hepatopathy, jaundice, bleeding diathesis and multi organ dysfunction. In severe falciparum malaria there occurs accelerated coagulation cascade activity with increased fibrinogen turnover, consumption of antithrombin-III and increased concentration of fibrin degradation product. In severe infection the prothrombin and partial thromboplastin time may be prolonged[3-6]. It has also been suggested that DIC is important in the pathogenesis of severe malaria. Coagulation cascade activity is directly proportional to disease severity but hypofibrinogenemia resulting from DIC is significant in approximately 5% of patient with severe malaria[7].

Hence this present study "COAGULATION PROFILE IN SEVERE FALCIPARUM MALARIA AND ITS CLINICAL CORRELATION" has been undertaken with the following objectives

- To study the effect of falciparum malaria on the coagulation cascade and correlate it with the cause and incidence of DIC.
- To correlate this altered coagulation parameters (PT, APTT) with degree of parasitemia and clinical severity
- To correlate alteration in the coagulation parameters with prognosis.

There were 2 major changes of platelet during malarial infection:

- Thrombocytopenia.
- Platelet dysfunction

Thrombocytopenia

The severe degree and higher incidence of thrombocytopenia were observed predominantly in complicated falciparum infection. Maximum thrombocytopenia occurred on the fifth or sixth day of infection and gradually returned to normal within 5-7 days after parasitemia ceased. The mechanism of thrombocytopenia in malaria is due to the immune mediated destruction of paletelets by reticuloendothelial system.

The activated platelets lost sialic acid from their membrane, resulting in intravascular lysis and thrombocytopenia. Further more consumption of platelets by the process of DIC was also another factor that contributed to thrombocytopenia in complicated P. falciparum malaria.

Platelet Dysfunction

During malarial infection 2 major changes in platelet function were demonstrated; platelet hyperactivity followed by platelet hypoactivity.

Platelet Hyperactivity

The evidence for hyperactivity of platelets during malarial infection comes from many studies. The lines of this evidence were hyperaggregation of platelets in response to small doses of ADP. There is also increase in thromboxane A_2 synthesis followed by release of platelet granules.

The stimulated platelets lost sialic acid from their membrane and became hyperactive. The intravascular lysis along with hyperaggregation accompanied by increased release of platelet granules induces fibrin thrombi formation and D.I.C.

Platelet Hypoactivity

This was demonstrated by decreased platelet aggregation on stimulation by various substances such as ADP, epinephrine and collagen. This abnormality occurred transiently and returned to normal within 7 to 14 days after parasitemia ceased.

As mentioned above hyperactive platelets released many substances from their granules, resulting in degranulated circulating platelets. The degranulated platelets became exhausted and lost their function. They became hypoaggregated and along with severe thrombocytopenia could contribute to the pathogenesis of bleeding in malaria.

MATERIAL & METHOD

The patient population included in this study was adult malaria patients aged 18 years and above, who had been admitted to dept. of medicine, MIMS during two year period from April 2010 to March 2012. The diagnosis of malaria was clinically suspected and later confirmed by examination of thick and thin smear / OptiMal test/ Quantitative Buffy coat (QBC).

The peripheral blood films were prepared from prick of finger, stained by conventional Leishman's stain and Geimsa stain seen under oil immersion (100×) and a minimum of 100 fields were examined before declaring the slides

negative for *Plasmodium* falciparum. All patients with previous coagulation disorders or disorders known to alter coagulation parameters were excluded from the study.

Hematologic investigations: complete blood picture (white and red blood cell count, hematocrit, hemoglobin and red blood cell indices) and coagulation profile (platlet count, PT, aPTT, BT CT were done immediately on admission repeated after 6-8 hrs. Repeat platelet counts were done in subjects with marked thrombocytopenia until normal or near-normal values were reached.

Platelet counts of 75,000 to 150,000/[micro]L are defined as grade 1 thrombocytopenia, 50,000 to <75,000/[micro]L as grade 2, 25,000 to <50,000/[micro]L as grade 3, and below 25,000/[micro]L as grade 4 thrombocytopenia. (CTCAE v3.0; www.ctep.cancer.gov/reporting/ctc.html) [20] .Subjects with a diagnosis of associated dengue fever and leptospirosis were excluded from the study, as both these conditions are known to significantly contribute to thrombocytopenia. FDP was done in patient who suspected to have DIC. Blood cells, hematocrit, hemoglobin, platelet count and blood film were checked on a daily basis after anti-malarial therapy until no evidence of active infection was found as indicated by the absence of schizont or ring stages from the blood films.

Cases with active infection by fifth day were followed at day seven and 14. Complete biochemical check up including renal and hepatic functions tests and serum electrolytes

Data collection: According to standardized procedure, we recorded the following information prospectively: (1) demographics (2) co-morbidities (3) presenting complaints at admission (4) bleeding manifestations (5) vital signs (6) biochemical profile, events and treatments during the course of treatment in case of hospitalized patients.

RESULTS

In this present study most patients belonged to age group of 25-44 years constituting 60%. Mean age of presentation was 32.92 with a male to female ratio of 1.85:1. Out of 387 cases studied 91 cases were selected. Of these 91 cases, 64% cases were infected with *P. falciparum (n=58)* whereas mixed infections (n=33) accounted for 36%. The complicated falciparum malaria accounts for 43% of cases (n=39).

Table 1: Platelet Count in Falciparum Malaria

Platelet Count	Complicated	Uncomplicated	Total	Percentage
Thrombocytopenia	37	30	67	73.63
Normal	2	22	24	26.37
Thrombocytosis	-	-	-	-
Total	**39**	**52**	**91**	**100**

Analysing the coagulation profile, it was observed that thrombocytopenia was present in 73.63% of cases (n=67) & 8 patients are having severe thrombocytopenia below 25000/cmm. Out of the 39 complicated cases, 6.59% (n=6) cases had detectable levels of fibrin degradation products.

Summarising the results, a total 73.63% cases showed thrombocytopenia, 8.79% had severe thrombocytopenia & in 6.59% of patients the PT , aPTT ,FDP was prolonged . Clinically 8.79%(n=8) of patients presented with bleeding manifestations.

DISCUSSIONS

Thrombocytopenia is a common feature of acute malaria and occurs . 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 severe malaria.

Severe haemorrhage is a feature of complicated falciparum malaria with a frequency of 5% (1,2,3). In present study bleeding manifestations were found in 8.79% (n=8) of patients. Degree of parasitemia is an important parameter as it correlates with the degree thrombocytopenia and coagulopathy. In the present study 76% had parasitemia less than 10% which is consistent with previous studies. Of the 91 cases 42,86 % (39cases) were associated with systemic complication and higher degree of parasitemia. This relative high incidence of complicated malaria is probably due to the fact that the study was undertaken in a tertiary centre.

In the present study thrombocytopenia was 73.6% (n=67) with the mean platelet count being 99.577/mm^3 which is compared with Richards et al[12] 1998 and Ladhani et al[9] 2002 with 67% and 56.7% of thrombocytopenia. The severe degree and higher incidence of thrombocytopenia were observed predominantly in complicated *P. Falciparum* infection. The mechanism of thrombocytopenia in malaria is mainly due to peripheral destruction and consumption.

In our series severe thromboctopenia was observed in 12.5% (n=11) cases. Out of 11cases 8 patients are having bleeding manifestations. So compared to incidence of thrombocytopenia (73.6%) incidence of bleeding manifestation is low (8.79%) indicating that bleeding manifestation is common in patients with low platelet count (<25,000).

The cases with bleeding manifestations was subjected to assessment of coagulation profile (PT,aPTT,FDP). It was observed that 6.59%(n=6) of cases had increased value of PT, aPTT and FDP indicating that these cases have disseminated intravascular coagulation(DIC) as the cause of thrombocytopenia. Punyagupta et al[11] 1974 also reported evidence of DIC in 100% cases having thrombocytopenia. The same mechanism was postulated earlier by Devakul et al[19], 1966 who reported that the platelets were being removed from circulation by consumptive coagulopathy.

These findings are in contrast to the findings of Beale et a1[1] 1972; Ladhani et al[9] 2002 all of whom reported that thrombocytopenia was not sole cause of DIC but other mechanism possible due to increased peripheral destruction or autoimmune mechanism. However detailed platelet kinetic studies will be required to establish such postulation.

In the present study bleeding time was found to be increased in 8 cases (8.79%) with a mean of 4.18 sec. which when compared with control group was statistically significant (P<0.05). All the cases had thrombocytopenia (100%).

N Jaroonvesama[7] in 1972 did his pioneering work of falciparum malaria and postulated that intravascular coagulation was an important intermediary mechanism in severe falciparum malaria. In the present study PT, APTT, FDP assays was done..

The Incidence was Lower than Studies of the Following Authors:

Name of Authors	Year of Observation	Incidence of Prolonged PT
Beale et al[1]	1972	15.15%
Sharma et al[13]	1992	6.67%
Rojanasthian S[17]	1992	76%

The large variation is due to different standards in different laboratories.

In the present study D-dimer which is a fibrin degradation product was detected qualitatively. The presence of D-Dimer represents the activation of coagulation cascade followed by activation of fibrinolytic system causing the fatal complication of DIC in malaria (Henry 11th edition). D-Dimer test was positive in 6.59% of cases in the present series.

The above Observation was Compared with the Following Authors:

Name of Authors	Year of Observation	Positivity of FDP
Dennis et al[5].	1967	75%
Neva et al[18]	1970	Very low
Beale et al[1]	1972	0%
Jaroonvesma[7]	1972	100%
Reid et al[16]	1972	100%
R.B. Skutowitz et al[14]	1973	0%
Punyagupta et al[11].	1974	Very high incidence
Vreeken et al[15]	1978	0%
Sharma et al[13]	1992	16.7%
Present Study	2004	6.59%

Phillips et al[11] 1986 observed that fewer than 10% of adults of cerebral malaria showed no clinical evidence of bleeding tendency with associated features of DIC, but laboratory activation of coagulation cascade was common. This observation is similar to the present study where incidence of DIC is 62.74%, but incidence of bleeding manifestation is only 10.78%.

It was observed that there was, significant alteration of coagulation parameters in falciparum malaria more so in the complicated cases.

REFERENCES

1. Beale PJ, Cormack JD, Oldrey TB 1972. Thrombocytopenia in malaria with immunoglobulin (IgM) changes. *BMJ 1*: 345-349.
2. Bergin J. Malaria and the lung. Military Med 1967;132:522-6.
3. Borochovitz D, Crosley A, Metz J. Disseminated intravascular coagulation with fatal hemorrhage in cerebral malaria. Br Med J 1970;2:710.
4. Cardoso M, Ferreira M, Camargo L, Szarfarc S. Anemia in a population from an endemic area of malaria, Rondonia (Brazil). Rev Saude Publica 1992;26:161-6.
5. Dennis L, Eichellberger J, Inman M, Conrad M. Depletion of coagulation factors in drug-resistant *Plasmodium falciparum* malaria. Blood 1967;29:712-21.
6. Gerardin P, Rogier C, KA Amadous S, Jouvencel P,Brousse V, Imbert P. Prognostic value of thrombocytopenia in African children with falciparum malaria. Am J Trop MedHyg 2002; 66: 686-91
7. Jaroonvesama N. Intravascular coagulation in falciparum malaria. *Lancet.* 1972 Jan 29;1(7744):221–223. [PubMed]
8. Kochar. D.K..,S. K.. Kochar, RP Agrawal, M. Sabir, K.C. Nayak, TD Agrawal, et al,2006. The changing spectrum of severe falciparum malaria, a clinical study from Bikaner (Northwest India). J. Vector. Brone Dis,43(3):104-8
9. Ladhani S, Lowe B, Cole AO, Kowuondo K, Newton CR.Changes in white blood cells and platelets in children with falciparum malaria: relationship to disease outcome. Br J Haematol.2002;119:839-47.
10. Phillips R, Pasvol G. Anemia of *P. falciparum* malaria Bailliere's Clin Hematol 1992;5:315-30.

11. Punyagupta S, Srichaikul T, Nitiyanant P, Petchclai B.Acute pulmonary insufficiency in falciparum malaria: summary of 12 cases with evidence of disseminated intravascular coagulation. Am J Trop Med Hyg 1974 Jul; 23(4):551-559
12. Richards, M.W., R.H. Behrens and J.F. Doherty, 1998.cases. Short report: hematologic changes in acute, imported falciparum malaria with spontaneous recovery on Plasmodium falciparum malaria. Am. J. Trop. Med. Hyg., 59: 859
13. Sharma SK, Das RK, Das BK, Das PK: Haematological and coagulation profile in acute falciparum malaria. *J Assoc Physicians India* 1992, 40:581-3. PubMed Abstract
14. Skudowitz, R.B., Katz.J., Lurie,A, Levin. J. And Metz.J (1973) Mechanisms of thrombocytopenia in malignant tertian malaria. Brit. Med. J., 2:515-518
15. Vreeken, J. And Cremer. Goote, T.M. (1978) haemostatic defect in non-immune patients with falciparum malaria; no evidence of diffuse intravascular coagulation. Br. Med. J., 2:533-535
16. Reid HA, Nkrumah FK: Fibrin-degradation products in cerebral malaria.*Lancet* **1**:218–221, 1972 | Article | PubMed | ChemPort |
17. Rojanasthien S, Surakamolleart V, Boonpucknavig S, Isarangkura P: Hematological and coagulation studies in malaria**.** *J Med Assoc Thai* 1992, **75**(Suppl 1)**:**190-194. PubMed Abstract
18. Neva, F. A., J. N. Sheagren, N. R. Shulman, and C. J.Canfield. 1970. Malaria: host-defense mechanisms and complications. Ann. Intern. Med. 73: 295-306.
19. Devakul K, Harinasuta T, and Reid HA. 125-I-labelledfibrinogen in cerebral malaria. Lancet 1966;2(7469):886-8.
20. Common terminology criteria for adverse events v 3.0 (CTCAE V.3.0). Available from: http://www.ctep.cancer.gov./reporting/ctc.html