A Study on Relationship of Hepatic and Renal Dysfunction with Haemorrheological Parameters in Plasmodium falciparum Malaria from a Tertiary Care Centre)

Dr.G.Balaraju[1], Dr. P.V. Rajasekhar[2], Dr. P. Ramulu[3], Dr. Komal[4]

[1]Dr.G. Balaraju M.D., Associate professor of medicine, Department of General Medicine, Osmania General Hospital, Hyderabad.
[2]Dr. P.V. Rajashekar M.D., Associate professor of medicine, Department of General Medicine, Osmania General Hospital, Hyderabad.
[3]Dr.C. Ramulu M.D., Professor of medicine, Department of General Medicine, Osmania General Hospital, Hyderabad.
[4]Dr. Komal M.D., Senior Resident of medicine, Department of General Medicine, Osmania General Hospital, Hyderabad.

***Abstract*- Objectives :** The present study was designed to assess hepatic and renal dysfunction in Plasmodium falciparum malaria, and evaluate if such abnormalities had any bearing with the hemorrheological dysfunction.

Methods : Thirty consecutive patients of Plasmodium falciparum malaria with hepatic and renal dysfunction (Group A) and thirty consecutive cases of uncomplicated falciparum malaria (Group B) were studied. Patients with past history of alcoholism, jaundice, chronic renal failure, bleeding diathesis or coagulopathy were excluded from the study. Laboratory investigations done were liver and renal function tests, complete blood count and coagulation profile. The data collected was analysed to inter – correlate parameters of hepatic, renal and hemorrheological dysfunction.

Results: Fever was the predominant feature in our study, present in 100% patient in both groups, followed by chills and rigors which was present in 90% in Group A and 86.67% in Group B. Hepatomegaly was present in 50% patients in Group A and 16.67% in Group B ,where as spleenomegaly was present in 40% in Group A and 20% in Group B. Most common complication in Group A was jaundice, present in 96.7% patients followed by renal failure present in 60% patients,cerebral malaria was present in 33.3% patients. Overt bleeding was present in only 1 patient (3.33%) with complicated falciparum malaria. Anemia was present in 70% of patients in Group A and 50% patients in Group B. Thrombocytopenia was present in 30% in Group A and 10% in Group B. Bleeding time was prolonged in 23.33% in Group A and 10% in Group B. Clotting time was prolonged in 30% in Group A and 15% in Group B.Prothrombin time is prolonged in 16.67% in Group A and 6% in Group B.The biochemical parameters (urea, creatinine ,bilirubin, AST, ALT, ALP) in both groups differed significantly. Hemoglobin and platelet count significantly negatively correlated with all the biochemical parameters FDP significantly positively correlated with all the biochemical parameters. In Group B the correlation between hematological and biochemical parameters was not found to be statistically significant.

Conclusion: Therefore, as revealed in our study, patients of complicated falciparum malaria have significant subclinical haemorrheological disorders even if they do not manifest as clinically overt DIC. Keeping in view, a significant number of such patients having renal failure, these subclinical hematological disorders adversely affect renal function contributing to acute renal failure.

***Index Terms*-** Plasmodium falciparum, hemorrheological, Hematological,renal, hepatic, PT, APTT

I. INTRODUCTION

Humanity has but three great enemies: Fever, famine and war; of these by far the greatest, by far the most terrible, is fever. Malaria is a protozoan disease transmitted by the bite of infected Anopheles mosquitoes[1]. Malaria is the major public health problem worldwide specially in South East Asian region, with nearly 1.2 billion people worldwide estimated to be at high risk[2]. Of the reported cases of malaria, India accounts for 66% (two thirds) of the cases in the South East Asian region[2]. Of these Orissa accounts for highest number of malaria cases in the country[3].

Of the four species of plasmodia causing human malaria, Plasmodium falciparum has the potential of developing life threatening complications, which may result in fatality. Not surprisingly in fatal cases malaria may be complicated with multiple organ dysfunction, the cumulative effects of which causes fatality[4].

Severe malaria is principally the result of Plasmodium falciparum infection which uniquely infects erythrocytes of all ages and mediates the sequestration of infected erythrocytes in small blood vessels, thereby evading clearance of infected RBC'S. The clinical pattern of malaria has changed worldwide including India in last decade[5].

Earlier cerebral malaria was the predominant manifestation of severe malaria whereas now the combination of jaundice and renal failure is more common[6].

The knowledge regarding the changing spectrum of malaria is very helpful for early diagnosis, because it may become untreatable and mortality is increased if the vital time is lost .

Studies on renal and hepatic dysfunction in Plasmodium falciparum malaria are aplenty , but there is a paucity of studies correlating haemotological abnormalities with hepatic and renal dysfunction in Plasmodium falciparum malaria.

The present study was designed to assess hepatic and renal dysfunction in Plasmodium falciparum malaria, and evaluate if such abnormalities had any bearing with the heamotological dysfunction.

II. AIMS AND OBJECTIVES

To study the clinical profile, renal and hepatic dysfunction and the relationship between renal and hepatic dysfunction with hematological parameters in falciparum malaria patients.

Materials and Methods

Present study was prospective observational study done on 60 patients who were malaria positive by smear/ immune chromotographic method, admitted in medical wards in Osmania General Hospital ,Hyderabad, Telangana From September 2012 -14. 30 malaria patients with renal and hepatic dysfunction(Group A) and 30 without any complication(Group B) were taken into study.

All malaria patients positive for Plasmodium falciparum by smear or immune chromatographic methods >15 years were included in the study. Malaria patients <15 years of age, positive for P.vivax and mixed infection, those with history of chronic liver disease, chronic renal failure, alcoholism, jaundice, bleeding diathesis and coagulopathy were excluded from the study.

Data was collected on standard proformas with detailed medical history, physical examination and investigations. Microscopy and smear for plasmodium species and RDT if required, hemoglobin, total and differential counts, platelet count, bleeding and clotting time, PT/APTT, FDP, random blood sugars, blood urea, serum creatinine, liver function tests : bilirubin with fractionation and enzymes were done in all patients. Blood culture and sensitivity, CSF analysis, chest X ray and ultrasound abdomen were done wherever found necessary.

STATISTICAL ANALYSIS: For continuous variables mean and standard deviation were calculated. The values obtained for each group were analyzed using the paired t-test to assess the significance. The correlation between different parameters calculated using two tailed pearson coefficient. A 'p' value of <0.05 is taken as a measure of significance. A 'p' value of <0.01 is taken as highly significant. QUICKCALC statistical software is used.

III. RESULTS

30 consecutive cases of Plasmodium falciparum malaria with hepatic or renal dysfunction or both (Group A), and 30 consecutive cases of uncomplicated falciparum malaria (Group B) were included as subjects. The age of the patients studied ranged between 15-70 years, with a mean age of 34.26years in Group A & 34.2 years in Group B. Majority of the patients were between 21 and 30 years

The incidence of malaria in males was more than in females which is shown in Figure1.

Clinical presentations encountered are summarized in Table 1. Laboratory parameters assessed, including haemorrheological parameters are summarized in Tables 2. The results of statistical analysis to deduce Pearson's correlation coefficient (2 – tailed) between LFTs, RFTs and haemorrheological parameters in Groups A and B are presented in Tables 3 to 6.

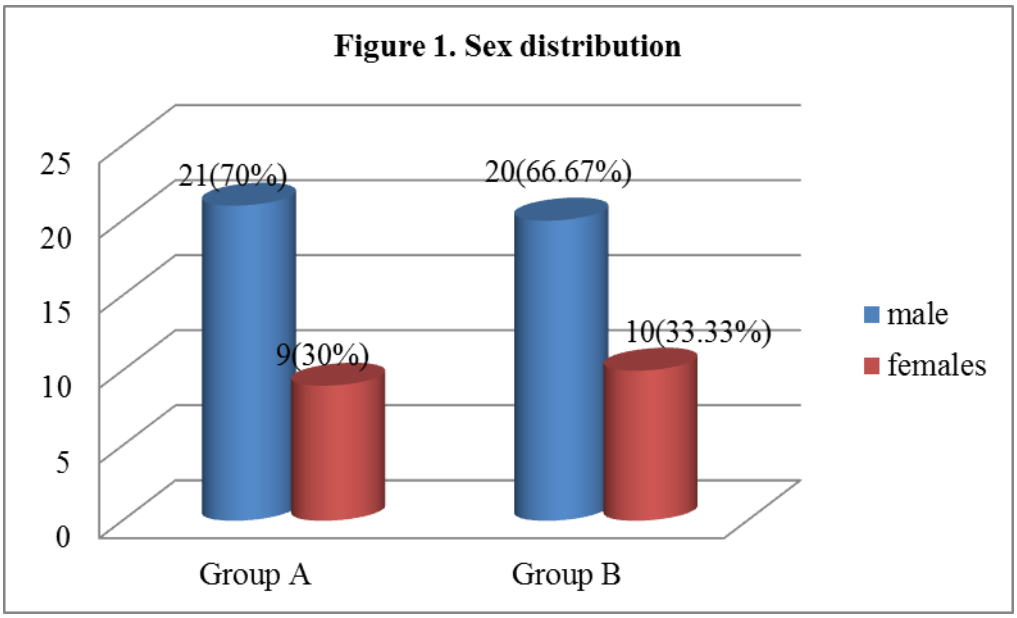

Table 1: Clinical features in falciparum patients :

Clinical features	Group A: Number & %	Group B: Number & %
Fever	30 (100%)	30 (100%)
Chills &rigors	27 (90%)	26 (86.67%)
Headache, myalgias	25 (83.33%)	18(60%)
Anemia	21 (70%)	15(50%)
Icterus	29 (96.67%)	-
Hepatomegaly	15 (50%)	5(16.67%)
Spleenomegaly	12 (40%)	6(20%)
Disorientation	10 (33.33%)	-
Convulsions	2 (6.67%)	-
Oliguria	18 (60%)	-
Respiratory distress	6 (20%)	-
Overt bleeding	1 (3.33%)	-

Table 2: Hematological and biochemical parameters in group A&B (mean values with standard deviation) and comparision with other studies

	Group A	Group B	Statistical significance	MISHRA et al STUDY
Hemoglobin(gm%	**9.87 ± 1.96**	**11.29±1.73**	**0.014(S)**	**0.42(NS)**
Platelet count	**1.80 ± 0.93**	**2.63±1.01**	**0.0019(S)**	**0.42(NS)**
Bleedingtime(sec)	**118.10±47.5**	**110.67±46.7**	**0.5986(NS)**	**0.14(NS)**
Clotting time(sec)	**486.67±181.3**	**412.21±151.2**	**0.167(NS)**	**0.11(NS)**
PT	**14.94±6.98**	**13.80±6.47**	**0.527(NS)**	**0.034(S)**

APTT	**38.89±14.70**	**36.31±13.24**	**0.417(NS)**	**<0.0001(S)**
FDP	**500.31±303.3**	**379.83±218.4**	**0.1023(NS)**	**0.0014(S)**
Urea (mg/dl)	**118.38±125.3**	**31.2±5.64**	**0.0009(S)**	**<0.0001(s)**
Creatinine	**3.35±3.42**	**0.92±0.18**	**0.0006(S)**	**<0.0001(s)**
Bilirubin	**12.26±7.83**	**0.76±0.29**	**<0.0001(S)**	**<0.0001(s)**
AST	**165.03±121.6**	**28.3±7.72**	**<0.0001(S)**	**<0.0001(s)**
ALT	**88.67±65.3**	**28.5±7.46**	**<0.0001(S)**	**0.0038(s)**
ALP	**139.03±78.95**	**79.90±19**	**0.0009(S)**	**0.0023(s)**

The biochemical parameters (urea, creatinine, bilirubin, AST, ALT,ALP) in both groups differed significantly.

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Table 3 :Correlation between hematological parameters renal function tests and liver function tests (group A)

		BILIRUBIN	AST	ALT	ALP	UREA
Hb(gm %)	r	-0.581	-0.485	-0.403	-0.411	-0.681
	p	0.0008	0.007	0.027	0.024	0.0000
Platelets	r	-0.638	-0.551	-0.469	-0.431	-0.580
	p	0.0001	0.0016	0.009	0.017	0.0008
BT	r	0.564	0.386	0.322	0.425	0.579
	p	0.0012	0.0353	0.082	0.019	0.0008
PT	r	0.430	0.484	0.506	0.367	0.092
	p	0.017	0.006	0.004	0.005	0.630
APTT	r	0.518	0.399	0.285	0.313	0.352
	p	0.003	0.028	0.127	0.092	0.056
FDP	r	0.590	0.646	0.567	0.5	0.541
	p	0.0006	0.0001	0.001	0.005	0.002

Hemoglobin and platelet count significantly negatively correlated with all the biochemical parameters. Bleeding time significantly correlated positively with Bilirubin, AST, ALP, Urea and creatinine but not with ALT. Prothrombin time significantly positively correlated with Bilirubin, AST, ALT, ALP , Creatinine but not with urea. APTT significantly positively correlated with bilirubin,AST and creatinine but not with ALT,ALP and Urea.

FDP significantly positively correlated with all the biochemical parameters.

Table 4: Correlation between hematological parameters, renal function tests and liver function tests (group B)

		BILIRUBIN	AST	ALT	ALP	UREA	CREATININE
Hb%	r	0.286	0.167	0.181	-0.046	-0.221	0.043
	p	0.125	0.377	0.340	0.810	0.240	0.822
PLATELETS	r	0.133	-0.0169	-0.065	-0.424	-0.108	0.209
	p	0.482	0.371	0.734	0.196	0.6445	0.268
BT	r	-0.120	-0.029	-0.068	0.053	-0.088	0.004
	P	0.529	0.879	0.722	0.779	0.645	0.982
PT	r	-0.135	0.074	0.031	0.143	0.033	0.069
	p	0.476	0.698	0.870	0.451	0.864	0.716
APTT	r	-0.168	0.017	-0.066	0.032	0.179	-0.123
	p	0.376	0.927	0.730	0.867	0.344	0.519
FDP	r	-0.170	-0.052	0.026	0.107	0.152	-0.110
	p	0.369	0.786	0.892	0.573	0.423	0.564

In our study in Group B the correlation between hematological and biochemical parameters was not found to be statistically significant. Similarly, serum ALP levels negatively correlated with BT but positively with both CT and APTT respectively.

Table 5: Correlation between renal function tests and liver function tests (group A)

		UREA	CREATININE
BILIRUBIN	R	0.625	0.695
	P	0.0002	0.0000
AST	R	0.443	0.445
	P	0.0141	0.0137
ALT	R	0.303	0.311
	P	0.104	0.095
ALP	R	0.459	0.483
	P	0.0123	0.0069

In our study, bilirubin, AST and ALP correlated positively with urea and creatinine but ALT did not correlate to the degree of significance.

Table 6: Correlation between renal function test and liver function test (group B)

		UREA	CREATININE
BILIRUBIN	R	0.024	-0.235
	P	0.900	0.210
AST	R	0.215	-0.089
	P	0.253	0.639
ALT	R	0.212	-0.015
	P	0.262	0.936
ALP	R	-0.060	-0.277
	P	0.754	0.138

In Group B bilirubin , AST, ALT, ALP did not correlate significantly with urea and creatinine.

IV. DISCUSSION

Thirty cases of *Plasmodium falciparum* malaria with hepatic or renal dysfunction or both (Group A), and thirty cases of uncomplicated falciparum malaria (Group B) were included as subjects. The age of the patients studied ranged between 15 and 70 years, with a mean age of 34.26 years in Group A and 34.2 years in the Group B. Maximum number of patients were in the age group 21-30 years. Falciparum malaria is usually a disease of the young due to their outdoor exposure and mobility. This observation is similar to other studies by DP Misra et al[3]., Das Sidhartha et al[6]., Kochar DK et al[7]., & Valluri Satya Prasad et al[8]., from India.

The incidence of malaria in males was more than in females due to working pattern the males are more exposed to mosquito bites outdoors.

We have found that the levels of hemoglobin and platelets and other hepatic and renal parameters (Table 2) significantly differed in both the groups of falciparum malaria similar to a study by Mishra et al[3].,.

In the present study hemoglobin and platelet count significantly negatively correlated with all the biochemical parameters. Association of hyperbilirubinemia with anemia is well recognised[4] and explained by increased red cell destruction occurring in complicated falciparum malaria[6,9]. Bleeding time significantly correlated positively with bilirubin, AST, ALP, Urea and creatinine but not with ALT similar to studies by DP Mishra et al[3]., and Hsu Wan-Ching, Lee et al[10]., Prothrombin time significantly positively correlated with bilirubin,AST,ALT, ALP , Creatinine but not with urea. APTT significantly positively correlated with bilirubin, AST and creatinine but not with ALT,ALP and Urea. The prolongation of BT, PT, APTT can be accounted for by the coagulopathy that was prevalent subclinically, and well recognised in patients with severe falciparum malaria[1,12]. The significant positive correlation between values of bilirubin and serum urea and creatinine has previously been reported[13]. FDP significantly positively correlated with all the biochemical parameters.

These findings are at par with those reported by previous investigators. In acute malaria coagulation cascade activity is accelerated with accelerated fibrinogen turnover, consumption of antithrombin III, reduced Factor XIII activity and increased concentration of fibrin degradation product. In severe infections, the prothrombin and partial thromboplastin times may be prolonged. This suggests, DIC is a major contributor for acute renal failure in these patients.

In our study, bilirubin, AST and ALP correlated positively with urea and creatinine but ALT did not correlate to the degree

of significance. The highly significant positive correlation between values of bilirubin and serum urea and creatinine ($p < 0.001$) has previously been reported by others from India. With increasing renal impairment there appears to be a fall in the renal excretion of conjugated bilirubin. This leads to a disproportionate rise in the plasma concentration of conjugated bilirubin, and this may further worsen the renal impairment since bilirubin can be toxic to renal tubules.

In Group B bilirubin ,AST,ALT,ALP did not correlate significantly with urea and creatinine.

Therefore, as revealed in our study, patients of complicated falciparum malaria have significant subclinical haemorrheological disorders even if they do not manifest as clinically overt DIC.

Keeping in view, a significant number of such patients having renal failure, these subclinical hematological disorders adversely affect renal function contributing to acute renal failure

V. SUMMARY AND CONCLUSIONS

Maximum number of patients affected were from younger age group that is 20-40 years due to their outdoor exposure and mobility. Males were affected more than females due to their more outdoor exposure to mosquitoes**.** Fever was present in all the patients (100%), but the characteristic paroxysm was rare. Other common sypmtoms were chills and rigors, myalgias, headache, hepato spleenomegaly. Most common complication was hepatic failure present in 96.7% patients followed by renal failure (60%). Overt bleeding was present in only 3.33% patient though the coagulation profile was deranged in large number of patients. The levels of hemoglobin and platelets significantly differed in both the groups of falciparum malaria. Other hematologicalparameters did not differ to the level of statistical significance. The biochemical parameters(Urea, Creatinine, Bilurubin, AST, ALT, ALP) in both the groups differed significantly. Hemoglobin and platelet count significantly negatively correlated with all the biochemical parameters. Bleeding time significantly correlated positively with Bilirubin, AST, ALP, Urea and Creatinine but not with ALP.

REFERENCES

[1] White NJ, Bregman JG et al., Malaria. Harrisons principles of Internal Medicine.18th ed .New york : McGraw-Hill companies 2012 ;1:1280-94.

[2] World malaria report 2013

[3] DP Misra, S Das et al., Relationship Of hepatic and renal dysfunction with hemorreogical parameters infalciparum malaria JAPI 2011 september;59

[4] Mahapatra MK , Sethi G,Das SP, Patnaikk SR . Incidence ,outcome and predictive factors of falciparaum malaria with multiorgan failure. JAPI 2001:49 :149-50.

[5] Nand N, Agarwal H, Sharma M, Singh M .Systemic manifestations of malaria. J Indian Academy of Clinical Medicine 2001 ;2:189-94.

[6] Das Sidhartha. Falciparum Malaria : a Multi-Systemic Disease in BK Sahay (ed), Medicine Update; Association of Physicians of India 2006;16:369-75.

[7] Kochar DK , Kochar SK , Agarwal RP . The changing spectrum of severe falciparum malaria:Aclinical study from bikaner(north west India).J Vect Borne Dis 2006 ;31(9):2278-84.

[8] Valluri Satya Prasad, Manavalla Subrahmanyam et al., Relationship of hepatic and renal dysfunction with haemorrheological parameters in plasmodium falciparum malaria J of Evidence Based Med & Hlthcare, pISSN- 2349-2562, eISSN- 2349-2570/ Vol. 2/Issue 18/May 04, 2015 Page 2470-2475

[9] M oxon CA, Heyderman RS, and Wassmer SC. Dysregulation of coagulation in cerebral malaria. Mol Biochem Parasitol. 2009;166:99– 108.

[10] Hsu Wan-Ching, Lee Fa-Yauh, Lee Shou-Dong. Prolonged bleeding time in cirrhotic patients: Relationship to peripheral vasodilation and severity of cirrhosis. J Gastroenterol Hepatol 2008;9:437-441.

[11] Francischetti IMB, Seydel KB, and Monteiro RQ. Blood Coagulation, Inflammation and Malaria.Microcirculation 2008;15:81 107.

[12] M ishra SK. Diagnosis, haematological and serological abnormalities in P. falciparum malaria in BK Sahay(ed): Medicine Update; Association of Physicians of India 2006;16:139-44.

[13] Pati SS, Mishra SK, Mohanty S, Pattnaik JK, Das BS. Influence of Renal Impairment on plasma concentration of conjugated bilirubin in cases of Plasmodium falciparum malaria. Ann Trop Med Parasitol 2003;97:581-6.

AUTHORS

First Author – Dr.G.Balaraju, Associate professor of medicine, Department of General Medicine, Osmania General Hospital, Hyderabad.

Second Author – Dr. P.V. Rajasekhar, Associate professor of medicine, Department of General Medicine, Osmania General Hospital, Hyderabad.

Third Author – Dr. P. Ramulu, Professor of medicine, Department of General Medicine, Osmania General Hospital, Hyderabad.

Fourth Author – Dr. Komal, Senior Resident of medicine, Department of General Medicine, Osmania General Hospital, Hyderabad.