

Evaluation of Liver Functions in Falciparum Malaria

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Abstract: Hepatic dysfunctions are well known to occur in severe falciparum malaria (PF); multiple factors are responsible for these. Acute renal failure in these patients is associated with poor prognosis. To evaluate hepatic and renal functions in patients of severe falciparum malaria (PF) and to find out the factors associated with poor outcome. Falciparum was present in peripheral blood film in 26 and in remaining 4 cases it was demonstrated by positive ICT. Beside routine investigations, hepatic and renal functions were carried out in each patient and were repeated on days 4 and 7th. Liver biopsy was done in 5 cases. The mean age of patients was 35.4 ± 12.8 years. There were 26 male and 4 female cases. Hepatic involvement was found in 19 patients with mean serum bilirubin of 7.5 ± 9.5 mg%. The jaundice was predominantly hepatic in 4, haemolytic in 7 and both hepatic and haemolytic in 8. All patients with jaundice had increased transaminases, which were >200 IU in 11 cases. Mean aspartate transaminase (AST) and alanine transaminase (ALT) were 168.1 ± 11.9 and 173.73 ± 158 IU, respectively. Prothrombin index was deranged in 13 patients, blood urea was raised in 24 cases and creatinine clearance was decreased in 22 cases; 18 cases had acute renal failure out of which 16 were jaundiced. Hyperparasitemia had a positive correlation with serum bilirubin ($r = +0.225$) as well as blood urea ($r = +0.495$). Liver biopsy revealed evidence of reticuloendothelial cell proliferation and hemozoin pigmentation. **Conclusions:** Hepatic and renal dysfunctions are common in falciparum malaria. Renal failure was seen more frequently in cases with hepatic dysfunction and heavy parasitemia. Multiple organ failure, severe anemia, thrombocytopenia, hepatic and renal dysfunctions were associated with poor outcome.

INTRODUCTION

In spite of phenomenal progress made in medical science, malaria continues to be major killer of mankind all over the world.¹ Falciparum malaria (PF) is one of the most important parasitic diseases of human being affecting more than one billion people and is responsible for 1 to 3 million deaths each year. Plasmodium infection retains its importance in present times and continues to pose a challenge to physician in view of its resurgence and atypical presentation. Pathophysiological mechanism of liver damage in falciparum malaria has been studied in past by many investigators.^{2,4} Factors responsible for jaundice in malaria are multiple including intravascular haemolysis of parasitized erythrocytes, liver dysfunction microangiopathic haemolysis associated with DIC and associated septicaemia.¹ Hepatic dysfunctions result from cytoadherence, rosetting and sequestration of erythrocytes containing mature forms of PF in deep vascular bed. These cases are more likely to have acute renal failure and their prognosis is bad. However there are few data available on prevalence of hepatic dysfunction in falciparum malaria in Indian context. Therefore, the present study was planned, to evaluate hepatic and renal dysfunction in present scenario in severe falciparum malaria.

MATERIAL & METHODS

The study was carried out on 30 admitted patients of severe malaria, who were found to be positive for plasmodium falciparum either in peripheral blood film or ICT test. The diagnosis of severe malaria was done according to WHO criteria.⁵ The **criteria** were: cerebral malaria (unarousable coma), severe anemia ($Hb < 5$ gm %), renal failure and serum creatinine (>3 mg %), pulmonary edema (ARDS), hypoglycemia (blood glucose < 40 mg %), circulatory collapse, DIC, repeated generalized convulsions, acidosis ($pH < 7.25$), macroscopic haemoglobinuria, hyperparasitemia ($>5\%$ of the RBC infected by parasite), serum bilirubin >3 mg%. Beside routine investigations platelet count, glucose-6-phosphatase dehydrogenase deficiency and fibrin degradation products were evaluated in each patient. Renal and hepatic functions were done on the day of admission and were repeated on days 4 and 7th. Liver biopsy was done in five patients to know the histopathological changes in falciparum malaria. Patient with preexisting liver disease like alcoholic liver disease, chronic active hepatitis, cirrhosis of liver, HBsAg positive patients, patients on ATT / hepatotoxic drugs, patients in whom the cause of hepatic dysfunction was secondary to infection like infectious mononucleosis, enteric fever and leptospirosis were excluded.

RESULTS

The mean age of patients was 35.4 ± 12.8 years. There were 26 male and 4 female cases. Alteration in sensorium was found in 19, oliguria in 9 and hemoglobinuria in 2. Jaundice was present in 19 patients. Splenomegaly was seen in 8, hepatomegaly in 17 and pallor in 28 (mean hemoglobin 6.89 ± 2.327 gm %). Hypoglycemia was found in 6 and metabolic acidosis was seen in 10 patients, where as electrolyte disturbances were seen in 26 cases. Prothrombin index was deranged 13 and it was $<75\%$ in 13 patients on the day of admission, in 7 cases on 4th day and in 2 cases on 7th day. Serum bilirubin was raised in 19 (mean 7.5 ± 9.5 mg %). The jaundice was predominantly hepatic in 4, haemolytic in 7 and combined in 8 patients. The serum bilirubin level on different days of admission is shown in Table-1. All patients with jaundice had increased transaminases and they were >200 IU in 11 cases. Mean AST and ALT were 168.1 ± 11.9 and 173.73 ± 158 IU, respectively (Table-2). Blood urea was raised in 24 and creatinine clearance was decreased in 22 cases. The mean creatinine clearance was 54.8 ± 35.47 ml/min on the day of admission, where as on day 4 and day 7 it was 56.8 ± 35.05 and on 64.2 ± 36.7 ml/min, respectively. A decrease in endogenous creatinine clearance (< 90 ml/min) was found in 22 patients (73.3%) on 0 day, in 20 and 17 patients on 4th and 7th day respectively. 18 cases had acute renal failure of which 16 were jaundiced. Hyperparasitemia had a positive correlation with serum bilirubin ($r = +0.225$) as well as blood urea ($r = +0.495$). Transient mild proteinuria (mean 0.56 ± 0.7 g/day) was seen in 15 and no case had nephrotic range proteinuria. Liver biopsy revealed evidence of reticuloendothelial cell proliferation and hemozoin pigmentation. Mortality was 33.3% and the patients who died, showed evidence of heavy parasitemia ranging from 15-40% (Table-3). Severe anemia was observed in five patients. All patients were comatose (Grade I-Grade IV). Four patients had evidence of thrombocytopenia. One patient had severe hyponatremia and four patients had evidence of mild hyponatremia. Evidence of hypokalemia was seen in four patients and one had evidence of hyperkalemia.

Table-1: Showing Serum Bilirubin (mg%) in falciparum malaria cases on different days of hospitalization

Day of Admission	>2mg - 5mg%	>5 - 10mg%	>10 - 15 mg%	>15 mg%
0 day	8	3	4	4
4 th day	2	4	2	5
7 th day	0	5	0	3
Total	10	12	6	12

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Table –2: Showing Serum Transaminases (IU) in falciparum malaria cases on different days of hospitalization

Day	SGOT 41-100 IU	SGPT 41-100 IU	SGOT 101-200 IU	SGPT 101-200 IU	SGOT >200 IU	SGPT >200 IU
0 day	10	6	8	6	11	11
4 day	8	8	9	0	6	10
7 day	11	10	1	1	3	3
Transaminases Mean±S.D.	168.1±119	173.73±158.45	139.4±122.6	157.5±162.6	95.6±92.5	88.76±123.984

Table-3: Clinical & biochemical parameters and prognosis in cases of falciparum malaria, who had hyperparasitemia >10%

Sr. No.	Age & Sex	Sensorium (Grade of coma)	Hb gm	Serum Bilirubin mg%	Parasite Index (%)	Blood Urea (mg%)	Serum Creatinine (mg%)	SGOT/SGPT (IU)	Outcome Expired/Recovered	Platelets
1.	32M	Grade II	9.4	8.0	15	190	2.6	328/611	Expired	Normal
2.	52F	Grade I	5.2	13.0	15	40	0.8	262/314	Recovered	Normal
3.	25M	Grade III	6.0	28.0	35	360	5.4	279/412	Expired	Decreased
4.	30M	Grade II	3.0	0.8	40	368	10.4	106/63	Expired	Normal
5.	35M	Grade I	7.6	0.8	12	20	0.8	48/28	Recovered	Normal
6.	30M	Grade II	3.9	5.4	14	98	2.6	245/203	Expired	Normal
7.	40M	Grade III	7.0	10.7	15	>500	3.5	204/254	Expired	Decreased
8.	28M	Grade I	9.0	22.0	25	20	2.8	286/142	Expired	Decreased
9.	27M	Grade IV	7.0	11.0	28	160	2.4	258/321	Expired	Decreased
10.	30M	Conscious	7.5	2.2	13	60	0.8	259/429	Recovered	Normal

Histopathological evidence of reticuloendothelial cell proliferation i.e. Kupffer cell hyperplasia was seen in three patients and hemozoin pigmentation was present in all the cases. Liver was congested with a grey / black pigmentation. Dilatation of hepatic sinusoids was seen in four patients, which were lined by Kupffer cells. One patient showed infiltration of portal triad with mononuclear cells. Malarial parasite was observed in hepatic sinusoids only in one case.

DISCUSSION

Jaundice is one of the common manifestations of severe falciparum malaria. Its incidence varies from 5.3 to 45% in different reports.^{6,9} It is multifactorial and occurs mainly due to intravascular haemolysis of RBC's, hepatic dysfunction and possibly due to microangiopathic haemolysis associated with DIC. While most patients have unconjugated hyperbilirubinemia, however conjugated bilirubin may predominate because of hepatocyte dysfunction. In jaundiced patients, there is increased vascular response to the catecholamines, increased plasma renin activity, uricosuria, natriuresis with failure to conserve sodium and left ventricular dysfunction.¹⁰⁻¹² Therefore, complications like acute renal failure is more frequent in jaundiced patients. Hepatomegaly is frequently seen in patients with PF however, hepatitis is seen in 2.5% of patients. Hyperplasia of reticuloendothelial cells is responsible for the enlargement of the liver.^{13,14} Tender hepatomegaly due to congestion is a common finding in all human malarials especially in young children and non-immune individuals.¹⁵

In the present study, two third patients had jaundice ranging from 2 to 38 mg/dl. It was predominantly conjugated in 4, unconjugated in 7 and mixed in 8. Hepatomegaly was present in 56.6% and splenomegaly was present in 26.6%. Out of 19 cases having jaundice, 21.05% had history of jaundice, altered sensorium and they were in coma Grade III – IV and 84.2% had ARF. There was a good positive correlation between hyperparasitemia and level of serum bilirubin. Thus a higher incidence of jaundice (63.3%) and hepatic failure (13.3%) seen in the present study was probably due to inclusion of more severe / complicated cases of malaria. The cause of jaundice was attributed mainly to intravascular haemolysis and hepatic dysfunction (42.1%), as reported by other workers.⁷⁻⁹

Malarial acute renal failure is multifactorial in origin. It is either due to direct effect of parasite on red blood cell (RBC) or due to non-specific effect of infection.¹⁵⁻¹⁷ Direct effect of parasite occurs after it attaches to specific receptor site on the cell membrane. Its maturation inside the RBC leads to alteration in the cell membrane and formation of electron dense protrusions

or knobs on its surface. The number of knobs increases as the parasite matures. This reduces the deformity of the RBC and enhances the adherence of RBC with the endothelial cell. Only falciparum infected RBC have this cytoadherence property.² This leads to occlusion of microcirculation in kidney leading to acute tubular necrosis. The non-specific effects of infection cause several pathophysiological alterations leading to renal ischaemia and acute tubular necrosis. Renal involvement in PF may vary from slight proteinuria to overt ARF and nephrotic syndrome.¹⁸ In the present study, mild proteinuria was seen in fifteen patients. A significant fall in proteinuria between on 7th day was seen in this study suggesting transient reversible glomerulopathy as its cause.

The cause of thrombocytopenia in malaria is not completely understood. Consumption of platelets as a part of disseminated intravascular coagulation has been suggested as possible mechanism. Excessive removal of normal or immunologically deranged platelets by hypertrophied reticuloendothelial system could be an alternative explanation. In uncomplicated cases of malaria thrombocytopenia occurs as a result of splenic pooling of platelets and moderate decrease in platelet life span.¹⁹ In the present study, derangement in platelet function was found in five patients. Only one patient showed prolongation of prothrombin time index. So, likely mechanism of thrombocytopenia in this study was splenic pooling. Since four of these patients died, therefore it would not be wrong to presume that thrombocytopenia is an adverse prognostic indicator.

Hyperparasitemia is an important determinant of mortality in severe malaria.²⁰ In this study, hyperparasitemia of more than 10% was observed in 12 patients. The degree of parasitemia varied from 5-40%. Statistical analysis of parasitemia revealed an excellent positive correlation of extent of hyperparasitemia with increase in blood urea (r=0.495) and serum bilirubin (r=0.225). All patients with high percentage of parasitemia (12) showed significant hepatic (n=10) (83.3%) and renal dysfunction (n=10) (83.3%). Therefore, results of this study revealed that hyperparasitemia was an important prognostic factor.

It can therefore, be concluded that hepatic and renal dysfunctions are common in falciparum malaria. Renal failure was seen more frequently in cases with jaundice and heavy parasitemia. Multiorgan failure, severe anemia, thrombocytopenia, hepatic and renal dysfunction were associated with poor outcome.

REFERENCES

1. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of Plasmodium falciparum malaria. *Nature*. 2005; 434: 214-17.
2. Roberts DD, Sherwood JA, Spitalnik SL, Pantone LJ, Howard RJ, Vishva MD et al. Thrombospondin binds falciparum malaria parasitized erythrocytes and may mediate cytoadherence. *Nature* 1985; 318(7): 65-6.
3. Clark IA, Cowden WB. The pathophysiology of falciparum malaria. *Pharmacol Ther*. 2003; 99: 221-60.
4. Anstey NM, Russell B, Yeo TW, Price RN. The pathophysiology of vivax malaria. *Trends Parasitol*. 2009; 25(5): 220-227.
5. Webe G, Schwarz ZE, Schlaefter F, Long R, Alkan M. Imported Severe falciparum Malaria in Israel. *J Travel Med* 1998; 5(2): 97-9.
6. Mishra SK, Mohapatra S, Mohanty S. Editorial. Jaundice in falciparum malaria. *J Ind Acad Clin Med* 2003; 4(1): 12-3.
7. Bhalla A, Suri V, Singh V. Malarial hepatopathy. *J Postgrad Med* 2006; 2:315-20.
8. Singh R, Kaur M, Arora D. A prospective study of hepatic involvement in plasmodium falciparum malaria. *Jour Clin Diag Res*. 2010; 4: 2190-2197.
9. Kochhar, D.K., Argawal, P., Kochhar, S.K., Jain, R., Rawat, N., Pokharm, R.K., Kachawa, S., Srivastava, T. Hepatocyte dysfunction and hepatic encephalopathy in Plasmodium falciparum malaria. *Q Journal of Medicine* 2003; 96: 505-512.
10. Yacoub S, Lang HJ, Shebbe M, et al. Cardiac function and hemodynamics in Kenyan children with severe malaria. *Crit Care Med*. 2010; 38(3):940-945.
11. Abro AH, Ustadi AM, Abro HA, Abdou AS, Younis NJ, Akaila SL. Jaundice with hepatic dysfunction in P. falciparum malaria. *J Coll Physicians Surg Pak*. 2009; 19: 363-6.
12. Premaratna R, Gunatilake AK, de Silva NR, Tilakaratne I, Fonseka MM, Desilva HJ. Severe hepatic dysfunction associated with falciparum malaria. *Southeast Asian J Trop Med Public Health* 2001; 32:70-72.
13. Gehlot RS, Ledha P, Baheti. Liver involvement in falciparum malaria - A histopathological analysis. *J Ind Acad Clin Med* 2003; 4(1): 34-5.
14. Mishra SK, Pati SS, Mahanta KC, Mohanty S. Rhabdomyolysis in falciparum malaria—a series of twelve cases (five children and seven adults). *Trop Doct*. 2010; 40(2): 87-88.
15. Radhakrishnan, J., Kiryluk. Acute renal failure outcomes in children and adults. *Kidney International* 2006; 69: 17-19.
16. Ekeanyanwu RC, Ogu GI. Assessment of renal function of Nigerian children infected with Plasmodium falciparum. *Int J Med Sci* 2010; 2:251-255.
17. Krishnan A, Karnad DR. Severe falciparum malaria: an important cause of multiple organ failure in Indian intensive care unit patients. *Crit Care Med* 2003; 31: 2278-84.
18. Nand N, Aggarwal HK, Sharma M, Singh M. Systemic manifestations of malaria. *J Ind Acad Clin Med* 2001; 2: 189-94.
19. Pascual CC, Kai O, Newton CR, Peshu N, Roberts DJ. Thrombocytopenia in falciparum malaria is associated with high concentrations of IL-10. *Am J Trop Med Hyg*. 2006; 75: 434-436.
20. Rao A, Kumar MK, Joseph T, Bulusu G. Cerebral malaria: insights from host-parasite protein-protein interactions. *Malar J*. 2010; 9: 155-63.