Original Article

Malarial Hepatopathy and Its Outcome in India

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Abstract

Background: Jaundice in *Plasmodium falciparum* malaria is multifactorial and its incidence varies in different regions. It is important to assess the incidence and factors associated with malarial hepatopathy as well as its complications to understand the pattern of disease presentation in order to undertake appropriate interventional measures. There is a paucity of data with regard to malarial hepatopathy and its outcome at the global level. **Aim:** The study was conducted to assess the pattern, spectrum of biochemical parameters and complications of hepatopathy related to *P. falciparum* malaria. **Materials and Methods:** A descriptive study was conducted in a tertiary care hospital attached to a government medical institution in Assam, India. Demographic details of the hundred patients with *P. falciparum* malaria, their clinical and biochemical parameters, complications and outcome were collected using a prestructured proforma. Data was compared using proportion and Chi Square test. **Results:** The proportion of those with malarial hepatopathy was 38% and the incidence was more in males and younger age group. The degree of hyperbilirubinemia, complications that include renal failure, shock, acute respiratory distress syndrome, hypoglycemia and mortality were significantly more among patients with hepatopathy ($P<0.05$). **Conclusion:** Malarial hepatopathy is associated with a higher incidence of complications like renal failure, shock, acute respiratory distress syndrome and hypoglycemia. Further studies are required to elucidate the factors associated with malarial hepatopathy and to prevent the complications and mortality.

Keywords: Falciparum malaria, Hepatopathy, India

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Introduction

Malaria is a major public health problem in India and is more common especially in North-Eastern states of India because of favorable environmental conditions. Currently changing trends with increase in the incidence and mortality related to *P. falciparum* malaria are observed.[1] *P. falciparum* malaria affects all age groups with multiple systemic complications which vary in different age groups. Hepatopathy is one of the complications of *P. falciparum* malaria. The manifestations of *P. falciparum* malaria are changing worldwide with respect to clinical presentation and complications.[2,3]

Access this article online

Quick Response Code:

Website: www.najms.org

DOI: 10.4103/1947-2714.101981

In the presence of *P. falciparum* infection with at least three fold increase in transaminase levels with or without conjugated hyperbilirubinemia and in the absence of clinical or serological evidence of viral hepatitis, the diagnosis of malarial hepatopathy is made.[4,5] There is a paucity of data related to malarial hepatopathy at the global level and a study of such nature will provide valuable information regarding the disease severity and outcomes, so that appropriate interventional measures can be adopted at an early stage. In view of the above, the present study is aimed to assess the pattern, biochemical parameters and outcome of hepatopathy related to *P. falciparum* infection in a tertiary care hospital in India.

Materials and Methods

This was a prospective cross sectional study done in Gauhati Medical College Hospital; Guwahati, India. The Institutional Ethical Committee clearance was taken before conducting the study. By taking minimum prevalence of hepatopathy as 20%[5] and precision at 40% level, total sample size was found to be 100.

Adult patients aged 15-60 years with the diagnosis of *P. falciparum* malaria from June 2006 to May 2007 were recruited. All the subjects were evaluated clinically, peripheral blood smear examination and/or antibody based rapid diagnostic testing to establish the diagnosis of *P. falciparum* malaria.

Those with acute viral hepatitis by history and serological studies, chronic viral hepatitis by history, clinical examination and/or laboratory evaluation, history of hepatotoxic drug intake in the recent past, history of intake of toxic herbal medicines for jaundice, history of alcohol consumption and coexistent *vivax* malarial infection were excluded from the study. Also subjects with symptoms and signs of leptospirosis and dengue were excluded by careful history and examination. IgM Anti-HAV, IgM Anti-HEV, HbsAg, and Anti-HCV were tested to rule out acute viral hepatitis. The diagnosis of malarial hepatitis was made if a patient fulfilled all the following criteria:[6]

1. Demonstration of *P. falciparum* infection by peripheral smear examination or antibody based rapid diagnostic testing.
2. At least three fold rise in transaminase levels (Alanine transaminase or Aspartate transaminase) with or without conjugated hyperbilirubinemia.
3. Absence of clinical or serological evidence of viral hepatitis.

The definitions and the criteria for severe malaria included clinical jaundice or a serum bilirubin of >3 mg/dL, renal failure with a serum creatinine of >3 mg/dL, hypoglycemia with a whole blood glucose concentration <40 mg/dL, shock with a systolic blood pressure of <90 mm Hg despite volume resuscitation and severe anemia with a hemoglobin of <5 g/dL.

Statistical analysis

The data was analyzed by proportion and Chi Square test using Statistical Package for Social Sciences (SPSS) version 11.0 software and *P* value less than 0.05 was considered to be significant.

Results

Out of 100 cases of *P. falciparum* malaria proven by peripheral blood smear examination and/Parasight-F test, 66 were males and 34 were females; the mean age being 29.51 years. All hundred patients had fever and 34% of the patients had clinical jaundice. Other clinical presentations included pain abdomen (42%), nausea and vomiting (35%), oliguria (24%), altered sensorium (24%), breathing difficulty (10%) and seizures (5%) on presentation. Bleeding manifestation was seen in 4 cases. Ultrasonography (US) showed hepatomegaly alone in 13 cases, splenomegaly alone in 8 cases and hepatosplenomegaly in 63 cases. Gall bladder wall thickening and sludge was seen in 11 patients on US.

Incidence of hepatopathy was comparatively more in males and younger age group [Table 1]. The proportion of those with hepatopathy was found to

Table 1: Demographic and baseline data of subjects with and without malarial hepatopathy (*N*=100)

Characteristics	Subjects with malarial hepatopathy	Subjects without malarial hepatopathy	*P* value
Age group			
15-19 (*N*=27)	12	15	0.075
20-29 (*N*=36)	15	21	
30-39 (*N*=24)	8	16	
40-49 (*N*=8)	2	6	
50-59 (*N*=5)	1	4	
Sex			
Male (*N*=66)	29	37	0.088
Female (*N*=34)	9	25	
Serum bilirubin levels (mg/dL)			
<1 (*N*=10)	2	8	<0.001*
1-2 (*N*=34)	5	29	
2-3 (*N*=22)	8	14	
3-10 (*N*=27)	18	9	
>10 (*N*=7)	5	2	
Systolic blood pressure (mmHg):Mean (SD)	86.4 (17.3)	96.8 (14.6)	0.0017*
Hemoglobin (g/dL):Mean (SD)	7.2 (3.9)	8.3 (4.5)	0.2155
Glucose (mg/dL):Mean (SD)	78 (56)	102 (45)	0.0205*
pH:Mean (SD)	7.19 (0.16)	7.34 (0.12)	<0.0001*
Creatinine (mg/dL):Mean (SD)	3.4 (1.9)	2.1 (1.4)	0.0002*

**P* value less than 0.05 is considered as significant

be 38%. 38 cases (38%) had >3-fold elevation of Serum Glutamic Pyruvic Transaminase (SGPT) and 36 cases (36%) had >3-fold elevation of Serum Glutamic Oxaloacetic Transaminase (SGOT). Overall, mean SGOT was 112.91 U/L and mean SGPT was 116 U/L. The maximum bilirubin level was 16.1 mg/dL and the mean value was 3.32 mg/dL. Among 38 patients with malarial hepatopathy with >3 times elevation of serum transaminases, 26 (68%) had predominantly direct hyperbilirubinemia and 12 (32%) had predominantly indirect hyperbilirubinemia.

Out of 100 cases, 28 (28%) had serum creatinine value of >3 mg/dL. Among the cases with malarial hepatopathy (38), 16 (42%) had serum creatinine value of >3 mg/dL. In the group without malarial hepatopathy (62), 12 (19%) had serum creatinine value of >3 mg/dL. The incidence of ARDS was 6 cases (15.8%) and 1 case (1.61%) in the group malarial hepatopathy and without malarial hepatopathy respectively. Also, the group with hepatopathy had more incidences of other complications like shock, severe anemia and hypoglycemia. The mortality was 34.2% (13 cases) in the group with hepatopathy and 8.1% (5 cases) in the group without hepatopathy [Table 2]. The complications like shock, acidosis and ARDS were associated with mortality and were more common in the group with hepatopathy [Table 3].

Table 2: Complications and mortality in malarial hepatopathy

Complications and mortality	Total number of subjects	Subjects with malarial hepatopathy (%)	*P* value
Renal failure			
Yes	28	16 (57.14)	0.014*
No	72	22 (30.56)	
Shock			
Yes	9	7 (77.78)	0.01*
No	91	31 (34.07)	
ARDS			
Yes	7	6 (85.71)	0.007*
No	93	32 (34.41)	
Hypoglycemia			
Yes	3	3 (100.0)	0.025*
No	97	35 (36.08)	
Severe anemia			
Yes	1	1 (100.0)	0.199
No	99	37 (37.37)	
Mortality			
Yes	18	13 (72.22)	0.001*
No	82	25 (30.49)	

**P* value less than 0.05 is considered as significant

Discussion

In the current study of *P. falciparum* malaria, all 100 patients had fever during hospitalization and 34% had clinical jaundice. This is in contrast to acute viral hepatitis, in which jaundice appears after the subsidence of fever. There is a wide variation in the incidence of jaundice in *P. falciparum* malaria with serum bilirubin levels ranging from 2.5 mg/dL to 62 mg/dL.[2,6] The probable explanations for this observation include the varying geographical conditions, endemicity of malaria in the region from which it is reported, the epidemic forms or the seasonal variations as well as the host factors.[2] The mean systolic blood pressure, glucose, pH and hemoglobin levels were lower in the group with hepatopathy in this study. The use of Multi-organ dysfunction score (MODS) is a simple way to assess the severity in *falciparum* malaria infection. The MODS score on admission which weighted clinical and laboratory parameters, highly correlated with the length of symptoms after admission and can be used to asses different levels of severity in *P. falciparum* malaria.[7]

In this study, 38 cases (38%) had malarial hepatopathy with >3 times elevation of serum transaminases, and among them 26 (68%) had predominantly direct hyperbilirubinemia. Previous studies have shown the incidence of hepatopathy ranging from 2.45% to 21%.[4-6] Reasons for this wide variation may be the different eligibility criteria, operational definitions and data collection methods used in various studies and the host factors. The higher incidence of hepatopathy in this study highlights the importance of elucidating the causes for the same including entomological research and host factors. There is a wide variation in the type of bilirubin which is elevated in malaria.[8-10] This could be due to either hemolysis or hepatopathy in the same condition, whichever is predominant. In contrast to other studies which reported predominantly unconjugated

Table 3: Cause of death in study subjects

Causes of death	Number (%) in the group with malarial hepatopathy	Number (%) in the group without malarial hepatopathy
Shock/circulatory failure	4 (30.8)	2 (40.0)
ARDS/respiratory failure	5 (38.5)	1 (20.0)
Hyperkalemia	2 (15.4)	1 (20.0)
Cerebral malaria	1 (7.7)	0 (0.0)
Sepsis	1 (7.7)	1 (20.0)
Cardiac	2 (15.4)	0 (0.0)
Acidosis	9 (69.2)	3 (60.0)
Total*	13	5

*Multiple causes in individual patients

hyperbilirubinemia,[9,10] majority (68%) of the cases in this study had conjugated hyperbilirubinemia. Hepatic dysfunction and jaundice in malaria are explained due to the failure of bilirubin excretion, endotoxemia, ischemia, acidosis or a combination of the above mentioned factors which may coexist in the same patient.[2] Jaundice in malaria could also be due to coexistent viral hepatitis, which should be excluded by serological studies. Alternative or herbal medicines commonly used in jaundice can contribute to hepatic dysfunction which may worsen the picture in severe malarial infection.

This study has shown a higher incidence of complications like renal failure, shock, acute respiratory distress syndrome and hypoglycemia in the group with malarial hepatopathy. This is in accordance with other similar studies in the past.[8,9] In another study, jaundice and hepatomegaly were significantly associated with renal failure and patients with acute renal failure had increased liver abnormalities compared with other groups.[11]

The mortality was higher in the group with malarial hepatopathy in this study. Similar observations were found in previous studies as well.[5,6,12,13] In India, mortality was 16.0% among adults, compared with 2.9% among children; cerebral malaria, severe anaemia, renal failure, and respiratory distress were highly statistically significantly related to fatal outcome in the regression analysis.[14] In another study from Bangladesh, India, Indonesia, and Myanmar, 53% were aged 21-50 years, and the overall mortality in *falciparum* malaria was 24% and varied on the basis of the site and treatment.[15]

Since this was a hospital based study, findings cannot be generalized to the community. Mild cases of malarial hepatopathy that visit the primary health care system may be missed, where the disease pattern and complications may be different. Liver biopsy and histopathology were not done in these subjects due to feasibility constraints. In spite of these limitations, the study provides valuable information which can be utilized by the concerned authorities of health care system for adopting appropriate interventional measures.

Conclusion

Malarial hepatopathy is associated with a higher incidence of complications like renal failure, shock, acute respiratory distress syndrome and hypoglycemia. Further studies are required to elucidate the factors associated with malarial hepatopathy and to prevent the complications and mortality. Secondary prevention by early diagnosis and treatment of *P. falciparum* malaria is also important in primary health care system in order to reduce the burden of malarial hepatopathy and its complications.

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How to cite this article: Saya RP, Debabrata G, Saya GK. Malarial hepatopathy and its outcome in India. North Am J Med Sci 2012;4:449-52.

Source of Support: Nil. **Conflict of Interest:** None declared.