

# Malarial Hepatopathy in Falciparum Malaria

Shahnaz Shah, Liaquat Ali, Rukhsana Abdul Sattar, Tariq Aziz, Tahir Ansari and Jamal Ara

## ABSTRACT

**Objective:** To evaluate the clinical, biochemical and sonographic changes in patients with falciparum malaria and jaundice.

**Study Design:** A case series.

**Place and Duration of Study:** This study was conducted at Medical Unit-I (Ward 5), Jinnah Postgraduate Medical Centre, Karachi, from January 2006 to November 2007.

**Methodology:** A total of 62 adult patients, regardless of age and gender, with peripheral blood film evidence of falciparum malaria, who had jaundice, were included. Any patient with evidence of infection with *Plasmodium vivax* or other causes of liver disease (e.g. viral hepatitis, cirrhosis, portal hypertension, amoebic liver abscess, unexplained hepatomegaly, ascites, history of alcoholism, taking hepatotoxic drugs, past history of jaundice) was excluded on the basis of history, relevant clinical examination and investigations.

**Results:** Age of the patients ranged from 13-48 years (mean 26.04±8.33). All patients were febrile and icteric, with pallor in 67.7%, hepatomegaly in 30.6%, splenomegaly in 70.9% and impaired consciousness in 20%.

Serum bilirubin levels ranged from 3 to 24 mg%. Thirty two (51.6%) had serum bilirubin 3-6 mg%, 20 (32.2%) had 6-10 mg% and 10 (16.1%) had >10 mg%. ALT levels ranged from 20-870 IU/L and AST levels 24-1210 IU/L respectively. INR ranged from 1-1.3. Twenty eight patients (45%) had predominantly conjugated or mixed hyperbilirubinemia and serum transaminases were more than three times normal. Ultrasonography revealed hepatomegaly with decreased echogenicity in 22 (35.4%), splenomegaly in 48 (77.4%) and both hepatomegaly and splenomegaly in 16 (25.8%). Gallbladder wall thickness was increased in 5 (8.06%) patients. There was no evidence of biliary dilatation.

**Conclusion:** A significant percentage of patients having falciparum malaria with jaundice fulfill the criteria for malarial hepatopathy. It should be considered in patients presenting with acute febrile illness with jaundice so that specific treatment can be given.

**Key words:** *Falciparum malaria. Malarial hepatopathy. Jaundice. Fever.*

## INTRODUCTION

Malaria is one of the leading causes of morbidity and mortality worldwide. It results in estimated 300-500 million new cases and 1.5-3 million deaths per year.<sup>1</sup> Yearly, approximately 30,000 travelers from the developed world are infected and several hundred die.<sup>2</sup> Infections that remain untreated can continue for upto 1.5 years. Infection leads to protective immunity which decays after several years, if re-infection does not occur. Falciparum malaria is a major community health problem in Pakistan.<sup>2</sup> It has high morbidity and mortality with varied manifestations, various presentations are not unusual, in fact more common.<sup>2</sup> The incidence of malaria is on the rise for the last two decades in Pakistan.<sup>3</sup> The cultural diversity and poverty present particular challenges.<sup>4</sup> Malaria is a highly complex disease, can mimic many diseases and there are no absolute diagnostic clinical features.<sup>5</sup> Clinical presentation of falciparum malaria may vary in

individuals depending upon the level of parasitemia and immune status of the patient.

Jaundice is one of the common manifestations of severe falciparum malaria. It is seen more in adults than children and may present alone or with other complications.<sup>6</sup> It results from the intravascular haemolysis of parasitized erythrocytes, hepatic dysfunction and possibly an element of microangiopathic haemolysis associated with disseminated intravascular coagulation. Severe jaundice associated with *Plasmodium (P.) falciparum* malaria is now a well-known entity, and high incidences are being reported from many countries of south-east Asia, but according to the WHO (2000) the signs of gross hepatocyte dysfunction and hepatic encephalopathy do not occur in these patients.<sup>7</sup> In recent years, there has been increasing number of reports favouring existence of malarial hepatopathy from Asian countries, especially from India.<sup>8,9</sup> The majority of the cases have either isolated infection with *P. falciparum* or a mixed infection with both *P. falciparum* and *P. vivax*.<sup>10,11</sup> Malarial hepatitis is a term commonly used to describe hepatocytic dysfunction in severe and complicated malaria.<sup>12</sup> It is characterized by a rise in serum bilirubin along with the rise in serum transaminase levels to more than three times the upper limit of normal.<sup>13</sup> This, in the absence of evidence of

Department of Medicine, Jinnah Postgraduate Medical Centre, Karachi.

**Correspondence:** Dr. Shahnaz Shah, B-6/551, Zeenat Arcade, Gul Mohor St., Garden East, Karachi.

E-mail: dr\_shahnaz1312@hotmail.com

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exposure to hepatotoxic drugs and absence of clinical or serological evidence of viral hepatitis makes malarial hepatopathy a unique entity.<sup>13</sup> Alteration in liver function had also been observed by many earlier workers in India, as well as other part of Asia, hence the present study was designed to determine the clinical, biochemical and sonographical changes in patients with falciparum malaria presenting with jaundice.

## METHODOLOGY

This study was conducted in Medical Unit-I (Ward 5), JPMC, Karachi, from January 2006 to November 2007. It included patients who had positive blood film for *Plasmodium (P.) falciparum* and were clinically jaundiced. Informed consent was taken and the purpose of the study was explained to patients/relatives. Data was entered on a pre-designed proforma.

Any patient with evidence of liver disease (e.g. viral hepatitis, cirrhosis of liver, portal hypertension, amoebic liver abscess, unexplained hepatomegaly, ascites, history of alcoholism, history of taking hepatotoxic drugs, past history of jaundice) was excluded on the basis of history, clinical examination and relevant investigations.

Detailed clinical examination was done in all patients. All patients underwent a set of investigations including complete blood counts, peripheral blood film for detailed morphology of RBCs, 6-9 thick and thin blood films for malarial parasites, bleeding time, clotting time, prothrombin time, total serum bilirubin, conjugated and unconjugated bilirubin and serum AST and ALT levels. Urine was examined for urobilinogen, bile pigment and bile salt. Blood culture and sensitivity, and blood tests for markers of hepatitis A, B, C, E and leptospirosis were done in all patients. To rule out any possibility of acute viral hepatitis, detailed serological investigations were done which included IgM anti-hepatitis-A-virus antibody (IgM anti-HAV), hepatitis B surface antigen (HBsAg), IgM anti-hepatitis-B-core antibody (IgM anti-HBc) and IgM anti-hepatitis-E-virus antibody (IgM anti-HEV). Detailed ultrasonography was done to check the size and echotexture of the liver, and to check for gallbladder abnormality, intrahepatic or extrahepatic biliary duct dilatation and signs of portal hypertension. Criteria used to diagnose malarial hepatopathy were demonstration of Plasmodium infection: *falciparum/vivax*, at least three-fold rise in transaminases (especially ALT, demonstrated in two samples, taken 24 hours apart, with or without conjugated hyperbilirubinemia, absence of clinical or serological evidence of viral hepatitis and response to anti-malarial therapy.<sup>12</sup>

## RESULTS

Age of the patients ranged from 13-48 (mean 26.04±8.33) years. Regarding clinical parameters, all

patients were febrile and icteric, other important findings included pallor in 67.7%, hepatomegaly in 30.6%, splenomegaly in 70.9% and impaired consciousness in 20%. Serum bilirubin levels ranged from 3 to 24 mg%. Thirty two (51.6%) had serum bilirubin of 3-6 mg%, 20 (32.2%) had 6-10 mg% and 10 (16.1%) had >10 mg%. ALT levels ranged from 20-870 IU/L and AST levels 24-1210 IU/L respectively. In 28 patients (45.16%), serum transaminase level was more than thrice the upper limit of normal levels and these patients had predominantly conjugated or mixed hyperbilirubinemia (Table I). INR ranged from 1-1.3. The most frequent sonological finding observed was hepatomegaly (Table I) with decreased echogenicity in 22 (35.4%) patients. It was seen in 16 (25.8%) patients with predominantly conjugated hyperbilirubinemia and 6 (9.6%) patients had mixed hyperbilirubinemia. In all the patients with hepatomegaly and/or decreased echogenicity on ultrasonography, transaminases were found to be more than thrice normal. There was no evidence of intrahepatic or extrahepatic biliary duct dilatation, portal hypertension or ascites.

**Table I:** Sonographic findings.

	Number of patients (n=62)	Percentage
Liver		
Enlarged liver	22	35.4
Decreased echogenicity (with hepatomegaly)	22	35.4
Decreased echogenicity (with normal sized liver)	6	9.6
Normal echogenicity and normal size	34	54.8
Increased wall thickness of gallbladder	5	8.06
Splenomegaly	48	77.4

## DISCUSSION

Falciparum malaria affect all ages with multiple systemic complications. Jaundice is one of the common manifestations of severe falciparum malaria. In patients with severe malarial infection, the incidence of jaundice is reported to be 2-57%.<sup>14</sup> Apart from intravascular haemolysis and disseminated intravascular coagulation, the authors have observed evidence of hepatocellular jaundice secondary to histopathological changes of liver in malaria as an important contributory factor. "Malarial hepatitis" or "malarial hepatopathy" is a term commonly used to describe hepatocytic dysfunction in severe and complicated malaria; however, actual inflammation of the liver parenchyma is almost never seen.<sup>12</sup>

Many workers have proposed the role of hepatocellular damage in patients having hyperbilirubinemia of greater magnitude. Bartelloni (1967) and Glor (1969) have suggested that mild jaundice may result from haemolysis alone, but very high bilirubin concentration indicate hepatocyte dysfunction.<sup>15</sup> According to the WHO, jaundice is one of the cardinal manifestations of severe malaria.<sup>7</sup> Intravascular haemolysis of parasitized and non-parasitized red blood cells has been

considered as an important factor in the causation of mild to moderate jaundice, but there the bilirubin is predominantly unconjugated and its levels do not rise very high.

There were 62 patients in this study with falciparum malaria having jaundice. Patients either had hepatomegaly or normal liver span on clinical examination and also on ultrasound which makes fulminant hepatic failure less likely in the presence of near normal coagulation profile. According to the WHO,<sup>7</sup> in severe falciparum malaria patients, serum bilirubin levels remain in the range of 7-10 mg%, but in this study 10 (16.1%) patients had serum bilirubin levels >10mg%. They had predominantly conjugated hyperbilirubinemia with elevated transaminases. Similar observation has been made in several other studies, specially in Asian countries. Haemolysis alone can produce only unconjugated hyperbilirubinemia which should not exceed >10mg%.

Regarding liver function tests, the maximum value of serum bilirubin observed in this study was 24mg% while in a study done by Kocher *et al.*, it was 48mg%.<sup>15</sup> In this study, 28 (45.16%) patients fulfilled the criteria for malarial hepatopathy, highest level of ALT and AST was 870 IU/L and 1210 IU/L respectively while in Kocher *et al.*'s study, it was 1120 IU/L and 1245 IU/L respectively.<sup>15</sup> Chawla *et al.* studied 31 patients, of whom 14 (45.16%) had serum bilirubin >10 mg%, with predominantly conjugated hyperbilirubinemia.<sup>16</sup> They attributed these elevated serum bilirubin levels to intravascular haemolysis and associated renal failure, leading to decreased excretion of bilirubin. Anand *et al.* studied 39 patients, out of whom, 13 (33.33%) had serum bilirubin in the range of 16±6.3 mg%, and most had predominantly conjugated hyperbilirubinemia.<sup>8</sup> In a study done by Ahsan *et al.* the incidence of jaundice was 46.05%, among whom, (57.14%) had bilirubin >10 mg/dl; mean serum ALT in patients with serum bilirubin 3-10 mg/dl, was 41±16 IU/L as compared to 53.46±31.24 IU/L in patients with serum bilirubin levels >10 mg/dl.<sup>17</sup> In a study done by Murthy *et al.* in 95 patients admitted with falciparum malaria, 20 (21.05%) had evidence of malarial hepatopathy.<sup>18</sup> Deller *et al.* also reported evidence of malarial hepatitis in patients of falciparum malaria with jaundice.<sup>19</sup> Debrito *et al.* in their study observed focal hepatocyte necrosis and linked it to the causes other than poor nutritional status.<sup>20</sup> In this study, the most common sonographic finding was hepatomegaly and decreased echogenicity of liver. In all those patients, transaminases were found to be more than thrice the upper limit of normal.

The observation of linear elevation of AST and ALT levels in patients with different bilirubin levels, hepatomegaly with low echogenicity and increased gallbladder wall thickness on ultrasound examination were important evidence of widespread hepatocyte

dysfunction in the absence of other causes of liver dysfunction. These patients fulfilled the criteria for malaria hepatopathy.

## CONCLUSION

Malarial hepatopathy is a well recognized entity which can be reliably diagnosed on the basis of clinical, biochemical and sonological parameters and should be suspected in patients with acute febrile illness, jaundice and raised transaminases. It should be differentiated from other conditions like acute hepatitis and fulminant hepatic failure so that timely and specific treatment could be given.

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