# Jaundice with Hepatic Dysfunction in *P.Falciparum* Malaria

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## ABSTRACT

**Objective**: To evaluate the frequency and severity of jaundice with hepatic dysfunction in Plasmodium (P.) falciparum malaria in adult patients admitted in the hospital.

Study Design: Descriptive study.

**Place and Duration of Study**: The Infectious Diseases Unit and Medical Wards at Rashid Hospital, Dubai, United Arab Emirates, from January 2005 to December 2007.

**Methodology:** This study included 105 adult patients who fulfilled the inclusion criteria. The diagnosis of *P.falciparum* malaria was confirmed by examination of thin and thick film stained with Leishman's stain. Other laboratory investigations included full blood count, liver function tests, blood urea, electrolytes, serum creatinine, reticulocyte count, blood sugar, viral hepatitis serology and coagulation profile. Patient with significant clinical/biochemical hepatic dysfunction were also subjected to ultrasonic examination of abdomen.

**Results**: On clinical examination, 23% patients were found to be jaundiced. Serum alanine amino transferase (ALT) level was above the reference range in 67.6%, but in only 11.4%, ALT was more than 3 times of normal level. Serum bilirubin was found to be higher than normal level in 81%, however, only in 23% of the patients, Serum bilirubin was >3mg/dl. Predominantly conjugated hyperbilirubinemia was observed in patients with high ALT. There was no significant change in serum albumin and prothrombin time. In comparison to normal bilirubin level, the patient with bilirubin >3mg/dl had high frequency of raised ALT 87.5% vs. 45% (p <.0001), thrombocytopenia 91.6% vs. 65% (p <.01), anemia 70.8% vs. 25% (p <.05) and renal impairment 50% vs. 20% (p >.05). Overall, 5 (4.7%) patients died and mortality rate was high among the patients with bilirubin level >3mg/dl than with normal bilirubin level 4 (16.6%) vs 1 (5%).

**Conclusion**: Hepatic dysfunction in acute *P.falciparum* malaria ranged from mild elevation of liver enzymes to acute hepatitis (ALT  $\ge 10$  times of normal level). It indicates severe illness with high frequency of complication and mortality rates.

Key words: Plasmodium falciparum. Jaundice. Hepatic dysfunction. Alanine transferase.

### **INTRODUCTION**

According to WHO data, approximately 270 million people suffer from malaria every year globally, with 1-2 million deaths annually, out of which 80% of the deaths are caused by *Plasmodium (P.) falciparum.*<sup>1</sup> Hepatic involvement in P.falciparum malaria is not an uncommon presentation and presence of jaundice (bilirubin >3mg/dl) is one of the indicators of severe malaria as defined by the WHO.<sup>2</sup> Jaundice in falciparum malaria may vary from mild to severe and is associated with high incidence of complications and mortality.<sup>3</sup> However, clinical signs of hepatic encephalopathy are unusual unless there is concomitant viral hepatitis. In comparison to acute viral hepatitis, recovery from jaundice and return of disturbed liver function tests to the reference range is usually faster in acute malaria. The patients with acute febrile illness and high bilirubin level with or without evidence of hepatic dysfunction

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should alert the physician to rule out acute malaria, particularly, if there is a history of recent travel to malaria endemic area.<sup>4</sup>

This study was conducted to evaluate the frequency and severity of jaundice with hepatic dysfunction in acute *P.falciparum* malaria in adult patients admitted in Rashid Hospital, Dubai, UAE.

#### METHODOLOGY

This was a hospital-based descriptive study conducted from January 2005 to December 2007 at Rashid Hospital, Dubai, UAE. The patients admitted in the Infectious Diseases Unit as well as in the medical wards of the hospital who fulfilled the criteria were recruited in the study. The study was designed to include the demographic (age, gender, nationality and history of travel), clinical information, biochemical and hematological changes observed in the patients. The data was entered into a structured proforma separately. The blood sample was obtained at the time of admission and the diagnosis of *P.falciparum* malaria was confirmed by examination of thin and thick film stained with Leishman's stain. Other laboratory investigations included full blood count, liver function tests, blood urea levels, serum creatinine and electrolytes levels,

reticulocyte count, blood sugar level, viral hepatitis serology and coagulation profile done for every patient. Patients with clinical/biochemical evidence of hepatic dysfunction were also subjected to ultrasonic examination of abdomen. In the patients with hepatic dysfunction, liver function tests were repeated every third day. Patients with clinical history and/or findings suggestive of chronic liver disease, drug induced hepatitis and reactivity to hepatitis B surface antigen, hepatitis C antibodies, hepatitis A IgM and hepatitis E IgM were excluded from the study. Management was done as per standard guidelines with Quinine Sulphate (IV/Oral) 20 mg/kg body weight stat dose followed by 10 mg/kg body weight in three divided doses for seven days. Unstable and patients with vomiting were treated by IV infusion, whereas others received oral Quinine Sulphate. On day three, almost all patients also received 3 Sulphadoxine+Pyrimethmine combination tablets stat. Patients were discharged from the hospital after significant improvement in clinical as well as hematological and biochemical parameters. Data was analyzed by SAS Enterprise Guide 4.1. Chi-square test was applied to compare the proportions of hyper bilirubinemia, thrombocytopenia, anemia and renal impairment between the patients with raised and normal ALT. P-value <0.05 was considered statistically significant difference between the proportions.

### RESULTS

A total of 105 patients fulfilled the inclusion criteria, 94 (91.5%) were males and 9 (8.5%) females. The mean age +SD of patients was 31.99+9.39 years (range 14-68 years). Except for the one UAE national, all the patients were expatriates who had visited or lived in the UAE. The majority of the patients were labourers. Out of the 105 patients, there were 57 (54.2%) Indians, 22 (21%) Pakistanis, 16 (15%) Africans and 10 (9.5%) other nationals. History of recent (within one month) travel to malaria endemic area was positive in 93 (88.4%) patients. The most common presenting symptoms were high-grade fever with rigors/chills, headache, vomiting followed by abdominal pain, impaired consciousness, cough and diarrhea. The duration of illness was 2-10 days before the patients presented to the accident and emergency department of the hospital. Clinical examination revealed anemia in 67 (64.7%), jaundice in 24 (23%), hepatomegaly in 44 (42%), splenomegaly in 40 (38%) and 9 (8.5%) patients were confused at the time of presentation (Table I).

Liver Function Tests (LFTs) showed increased ALT in 71 (67.6%) patients above the reference range, with mean ALT levels  $57.92\pm71U/L$ , but in 12 (11.4%) patients, it exceeded 3 times of normal levels (maximum 462 U/L). Bilirubin level was raised above the normal level in 85 (81%) patients, with mean bilirubin level of 2.45 $\pm$ 2.22 mg/dl. In 24 (23%) patients, bilirubin was

 Table I: Clinical, biochemical and hematological profile of the patients.

Parameters	Number of	Percentage of	
	patients	patients	
Clinical			
Male	94	91.5%	
Female	9	8.5%	
Fever	103	98%	
Anemia	67	64.7%	
Jaundice	24	23%	
Confusion	9	8.5%	
Hepatomegaly	44	42%	
Splenomegaly	40	38%	
LFTs*			
Normal ALT	35	33.3%	
Raised ALT>3 times	12	12.4%	
Normal Bilirubin	20	19%	
Raised Bil >3 times	24	23%	
FBC*			
Anemia	67	64.7%	
Thrombocytopenia	91	86.6%	
Normal WBC	90	85.7%	
S.Creatinine*			
Increased S.Creatinine.	38	36.1%	

\*Ref.ranges:ALT-0-31U/L,Bil.0-1mg/dl,S.Creat .5-1mg/dl,Hb%.13-18gm/dl, WBC 3.6-11x10<sup>3</sup>cell/ul,Plat.150-450x10<sup>3</sup>cells/ul.

>3mg/dl (maximum-11.4 mg/dl). The patients with increased ALT level had predominant conjugated hyperbilirubinemia, whereas patients with normal liver function tests had un-conjugated hyperbilirubinemia. There was no significant change in the levels of serum albumin and prothrombin time. None of the patient had evidence of fulminant hepatic failure. Thrombocytopenia was present in 91 (86.6%) patients with mean platelet count  $87.43\pm68.4\times10^3$  cells/ul. Anemia was found in 68 (64.7%) patients with mean Hb% 11.44 $\pm$ 3 gm/dl. WBC count was normal in 90 (85.7%) and only 6 (5.7%) patients had leucocytosis. Creatinine was increased in 38 (36.1%) patients with mean serum creatinine level of  $1.8\pm0.8$  mg/dl (maximum-6.7mg/dl, Table I).

In comparison to normal bilirubin level, the patients with bilirubin level >3mg/dl had high incidence of raised ALT-87.5% vs. 45% (p <0.001), thrombocytopenia - 91.6% vs. 65% (p <0.01), anemia - 70.8% vs. 25% (p <0.05) and renal impairment - 50% vs. 20% (p >0.05). A total of 5 (4.7%) patients died due to cerebral malaria and severe malaria leading to multi-organ dysfunction. The mortality rate was observed as higher among the patients with raised bilirubin level (>3mg/dl) than those with normal levels 4 (16.6%) vs. 1 (5%).

## DISCUSSION

Malarial hepatitis is a term commonly used to describe hepatocytic dysfunction in severe and complicated malaria. Malarial hepatitis is characterized by a rise in serum bilirubin along with the rise in serum glutamate pyruvate transaminase levels to more than three times the upper limit of normal.<sup>5</sup> The incidence of jaundice and hepatocellular dysfunctions in severe malarial infection have been reported variably, which may be due to the

geographic conditions, endemicity of malaria in the region from where the reports have originated, the age groups studied, the epidemic form of infections reported and coexistent viral hepatitis or helmenthic infections endemic to that particular area.<sup>6</sup> The incidence of jaundice is seen more in adults7 and it varies from 32-37% with predominant unconjugated hyperbilirubinemia as reported by Harris at al.,8 but jaundice with hepatic dysfunction is also common in children with incidence as high as 32%.9 In this case series, jaundice was present in 23%, a percentage significantly higher than reported by Mehta et al. (2.5%)<sup>10</sup> and Anad et al. (5.3%).<sup>5</sup> However, Murthy et al., reported jaundice in 62%<sup>3</sup> and in another study of 121 cases of malarial infection from Poland, about 37% of the patients demonstrated symptoms of hepatic parenchymal dysfunction.<sup>11</sup> Kockar et al. has reported that in P.falciparum malaria, the serum bilirubin is elevated and it is the conjugated fraction which is dominant in patients who develop hepatic dysfunction and liver enzymes are elevated 2-3 times the normal and may be much beyond this level.<sup>12</sup> The present findings are consistent with the above study as we also noted dominant conjugated hyperbilirubinemia in those patients who had deranged LFTs and in 11.4% of the patients, ALT was >3 times of normal level.

The presence of hepatitis in patients with falciparum malaria indicates a more severe illness with a higher incidence of complications and a poor prognosis. In this case series, the patients with serum bilirubin >3mg, 50% of them developed acute renal impairment as compared to 20% with normal bilirubin level and, we also observed higher mortality rate (16.6% vs. 5%) in jaundiced patients, an observation which is also supported by other studies.<sup>3</sup> In this study, we noted higher incidence of thrombocytopenia (91.6 vs 65%) and anemia (70.8 vs. 25%) in patients with jaundice with hepatic dysfunction as compared to normal bilirubin level and liver function, Kockar et al.12 also had the same observation. In another study, thrombocytopenia was also documented in 89.13% patients suffering from acute renal failure and jaundice due to P.falciparum malaria.13 Severe coagulopathy is almost never seen in isolation with severe malaria and prothrombin time is usually within normal limits even in patients with marked elevation of liver enzymes.14 In this case series also, no significant disturbance was observed in the coagulation profile.

Jaundice in severe *P.falciparum* malaria is multifactorial; intravascular haemolysis of parasitized red blood cells, haemolysis of non-parasitized red blood cells (innocent bystanders), hepatic dysfunction, associated haemoglobinopathies and drug induced haemolysis (including Quinine).<sup>7</sup> The other causes of jaundice in malaria could be coexistent with viral hepatitis, especially infections with hepatitis E virus or hepatitis A virus.<sup>15</sup> Underlying chronic liver disease due to hepatitis B virus has been reported to be a risk factor for severe malarial infection and their coexistence may result in exaggerated hepatocyte dysfunction.<sup>6</sup> Disseminated intravascular coagulation may also contribute to hepatocellular dysfunction seen in severe malarial infection.<sup>16</sup> Although glucose 6 phosphatase deficiency (G6PD) may be protective against the development of severe malarial infection per se and/or antimalarial drugs used in these G6PD deficient patients may precipitate haemolysis and result in jaundice in these patients.<sup>17</sup> However, in acute malaria, hepatic dysfunction is reversible in all the patients developing malarial hepatopathy who respond favourably to antimalarial therapy and no residual effects have been documented in survivors.18 Bilirubin normally recedes by 72 hours of starting treatment but it may be delayed in patients having coexisting renal dysfunction.<sup>19</sup> In this study, we also noted significant improvement in liver function test with malaria treatment and bilirubin and ALT reduced to reference range in almost all of the patients at the time of discharge but the patients with renal impairment had longer hospital stay and slower improvement in liver function tests.

### CONCLUSION

In conclusion, in this study, we observed that liver is commonly involved in acute *Pfalciparum* malaria, and hepatic dysfunction ranges from mild elevation of liver enzymes to the range of acute hepatitis (ALT $\geq$ 10 times of normal levels). Furthermore, it was also noted that hepatic dysfunction with jaundice is a serious development in acute *Pfalciparum* malaria and it indicates severe illness with higher incidence of complication and mortality. For better outcome, these patients should be treated promptly and optimally.

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