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# Malarial hepatitis: A heterogeneous syndrome?

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## ABSTRACT

*Background.* The incidence of malarial hepatitis in patients with *Plasmodium falciparum* infection and jaundice is not known and it is not clear whether the condition is a single entity or a heterogeneous syndrome.

*Methods.* We prospectively studied the natural history of all patients with falciparum malaria and jaundice admitted to military hospitals in Northeast India from 1988 to 1991. A possible drug or viral cause for the hepatitis was excluded by the history, serological tests and liver histology.

*Results.* Of the 732 patients admitted with falciparum malaria, 39 had jaundice but only 18 had malarial hepatitis indicated by a rise in their serum glutamate pyruvate transaminase levels to more than three times the upper limit of normal and an absence of clinical or serological evidence to suggest drug or viral hepatitis. The liver in these patients was always enlarged. Their mean age was 27.6 years and 85% were males. The mean serum bilirubin was 12.7±10.3 mg/dl, serum glutamate oxaloacetate transaminase was 212.8±144.9 IU, serum glutamate pyruvate transaminase was 287.1±206.2 IU and the serum alkaline phosphatase was 20.4±10.1 KA. Clinically, 2 groups of patients were seen. Thirteen patients who presented with a severe form of disease had coma, deep jaundice and renal failure. The other 5 patients had a relatively mild illness with only fever, headache and vomiting for 2 days. Four patients with severe disease died. Liver histology (studied in 5 patients) showed Kupffer cell hyperplasia and deposition of malarial pigment. *Plasmodium falciparum* was demonstrated in sinusoidal red blood cells in only 2 cases.

*Conclusions.* Malarial hepatitis occurred in 18 out of 39 patients with jaundice and falciparum malaria. It is a heterogeneous syndrome with at least two clinical subsets and the severe disease should not be mistaken for fulminant hepatic failure as there is a better response to therapy.

## INTRODUCTION

The presence of jaundice in a patient with malaria can be due to intravascular haemolysis, disseminated intravascular coagulation and rarely to malarial hepatitis.[1] Alterations in hepatic function have rarely been recorded in malaria, even though primary schizogony of the malarial parasite always leads to rupture of the infected hepatocyte.[2] The term 'malarial hepatitis' has been used to describe hepatocellular jaundice in patients with *Plasmodium falciparum* infections.[3–5] We prospectively studied all patients with malaria and jaundice to determine their natural history.

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## PATIENTS AND METHODS

Seven hundred and thirty-two patients with *P. falciparum* malaria were admitted from 1988 to 1991 in 5 military hospitals in Northeast India. Of these only 39 (5.3%) patients had jaundice. After a careful history and physical examination, all the patients had complete blood counts, peripheral blood smear examination, estimation of blood sugar and urea, serum creatinine, uric acid and electrolytes. Liver function tests included determination of the serum bilirubin, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), serum alkaline phosphatase (SAP), serum proteins and prothrombin time. These were repeated at 1 to 3 day intervals depending upon the patient's condition.

Liver biopsies were done in 1 patient who survived and in 4 cases during post mortem examination. The diagnosis of *P. falciparum* malaria was made by demonstrating asexual forms of *P. falciparum* in the peripheral blood smear. The hyperbilirubinaemia was considered predominantly conjugated if the directly reacting fraction was more than 50% of the total bilirubin and predominantly unconjugated if the indirectly reacting fraction was more than 80% of the total. Patients with levels in between were regarded as having mixed hyperbilirubinaemia. A diagnosis of malarial hepatitis was made in patients who had

1. Falciparum malaria
2. A more than 3-fold rise in SGPT demonstrated on at least 2 consecutive blood samples
3. Absence of clinical or serological evidence to suggest viral and drug hepatitis
4. Clinical response to anti-malarial drugs or autopsy demonstration of disseminated falciparum malaria.

Of the 39 patients, 27 received quinine and tetracycline while the remaining 12 also received a combination of sulfadoxin and pyrimethamine.[6] Hepatitis was considered to have remitted when icterus disappeared and the transaminase levels returned to normal.

## RESULTS

All 39 patients were transferred to our referral gastroenterology centre, 2 to 7 days after their initial presentation (mean 3.8 days). Their mean age was 27.6 years (range 22 to 46) and 33 (85%) were males. The mean of the highest bilirubin levels was 9.3 (range 2.1 to 23.4) mg/dl. Unconjugated hyberbilirubinaemia was present in 19 patients, conjugated in 14 and mixed in 6.

In 18 patients the transaminases were greater than thrice the normal values and these formed the study group of patients with malarial hepatitis. In 14 of these the hyperbilirubinaemia was conjugated while in 4 it was mixed. All those with mixed hyperbilirubinaemia had evidence of intravascular haemolysis in the form of haemoglobinaemia and haemoglobinuria in addition to raised transaminase levels. Jaundice was noted at initial presentation in 12 patients and 1 to 5 days later in the remaining 6. The derangements in liver function are shown in Table I.

TABLE I. Hepatic and renal functions in patients with malarial hepatitis.

| | All patients $n=18$ | Group A $n=13$ | Group B $n=5$ |
|---|---|---|---|
| Serum bilirubin (mg/dl) | 12.7±10.3 | 16.1±6.3 | 3.9±1.9 |
| SGOT (IU) | 212.8±104.9 | 256.8±154.5 | 98.2±43.8 |
| SGPT (IU) | 287.1±206.2 | 351.9±239.4 | 118.6±72.1 |
| SAP (KA) | 20.4±10.1 | 22.8±9.6 | 14.3±5.6 |
| Total proteins (g/dl) | 6.7±0.8 | 6.8±0.8 | 6.6±0.5 |
| Serum albumin (g/dl) | 3.9±0.7 | 3.9±0.6 | 3.8±0.5 |
| Blood urea (mg/dl) | 109.6±96.6 | 138.7±86.2 | 34.1±8.4 |
| Creatinine (mg/dl) | 4.2±2.4 | 5.4±2.1 | 1.1±0.5 |
| Prothrombin time (seconds more than control) | 6.3±3.8 | 5.7±4.0 | 4.2±1.8 |

all values are mean±SD of the maximum values during the course of the disease
SGOT serum glutamate oxaloacetate transaminase
SGPT serum glutamate pyruvate transaminase SAP serum alkaline phosphatase

The initial diagnosis was cerebral malaria in 13 out of 18 patients with malarial hepatitis. They had a fulminant clinical illness (Group A) with deep jaundice, purpura and coma, and developed evidence of renal failure within 72 hours of admission. The other 5 patients had a relatively mild illness (Group B) and presented with high grade fever, severe headache and vomiting for less than 2 days. Examination of the peripheral smear showed *P. falciparum* in all these patients. None of those with a mild illness developed coma or renal failure though one patient had transient delirium and was diagnosed to have cerebral malaria. Figure 1 compares the clinical profile of a typical patient from each of the groups.

The hepatitis remitted in a mean of 22.8 (range 18 to 29) days in group A and in 11.7 (range 5 to 23) days in group B. While 4 out of 13 patients died in group A, there was no death in group B. There was no evidence of residual hepatic damage in the survivors at 8 weeks and 6 months ($n=12$) of follow up. 2 patients were lost to follow up at 6 months. Liver histology (5 patients in group A) showed Kupffer cell hyperplasia and deposition of malarial pigment in 4 (Fig. 2). There was portal infiltration by chronic inflammatory cells in 3, sinusoidal infiltration in 2 and features of intrahepatocytic cholestasis in 2. Focal spotty necrosis and centrizonal necrosis was seen in 1 patient each. Malarial parasites in the red blood cells were seen in the histological sections of only 2 patients.

## DISCUSSION

Hepatitis in relation to falciparum malaria has been reported infrequently.[3,7,8] Our data indicates that it is not an uncommon entity and in endemic areas is seen in about 2.5% of patients with falciparum malaria. It also appears to be a heterogenous syndrome and we encountered 2 clinical subsets of patients. In one group, there was an acute, virulent presentation with coma, renal failure and in some cases even haemorrhagic manifestations. It is only in this setting that jaundice signified a 'severe' disease as noted by the WHO action programme.[1] This presentation is often confused with acute viral hepatitis and fulminant hepatic failure in non-endemic areas.[3,9]

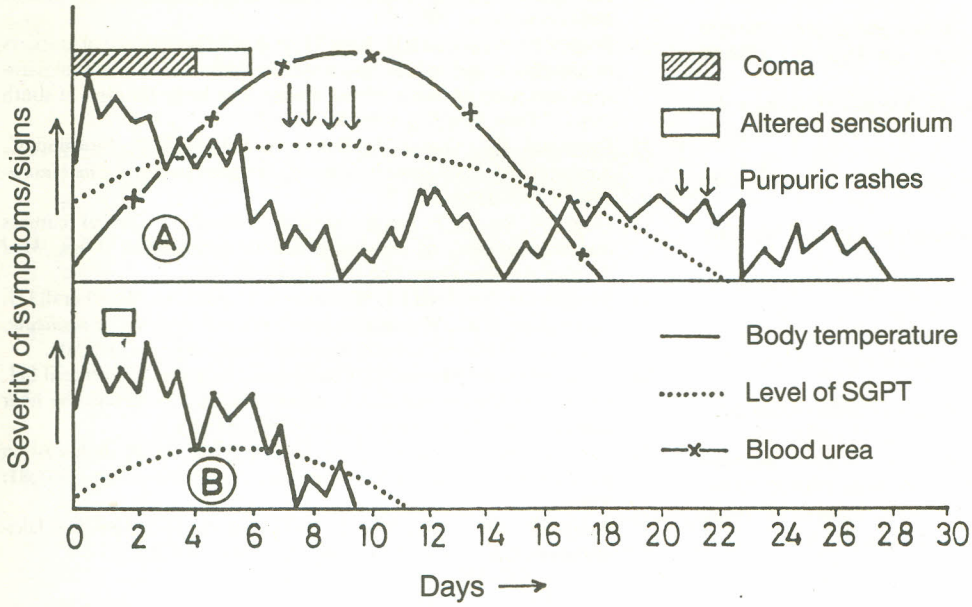
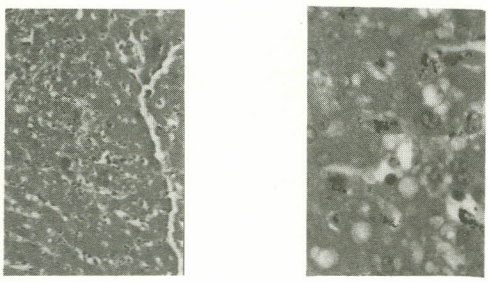



FIG 1. Comparison of clinical course of a typical patient from group A with that of another from group B



A. Reticuloendothelial hyperplasia (× 250)

B. Malarial pigment deposition (× 450)

FIG 2. Malarial hepatitis

Clinically patients with malarial hepatitis always have an enlarged liver and show a good response to anti-malarial therapy. Massive hepatic necrosis does not occur in malarial hepatitis. In the second group, the presentation was of a mild episode of uncomplicated hepatitis and this corresponds to the usual description of this entity in textbooks.[10]

Although 'malarial hepatitis' has been used to describe the occurrence of hepatocellular jaundice in patients with falciparum malaria,[3,4,7] the exact aetiology of the jaundice is not yet clearly understood. Malaria can rarely coexist with viral hepatitis[11] but we excluded this possibility by conducting serological tests. The possibility of coincidental non-A, non-B hepatitis can probably be ruled out by the histological findings seen in our patients. For the same reason, hepatitis due to anti-malarial drugs[12,13] was also unlikely to have been the cause of jaundice. Jaundice in falciparum malaria (seen in 5.3% of patients in this study) has been more often associated with haemolysis than hepatocellular damage. While raised SGOT levels may be caused by haemolysis, elevations in SGPT are more specific for malarial hepatitis. However, intravascular haemolysis and malarial hepatitis can coexist as was seen in 4 of our patients.

The characteristic histological abnormality described in patients with malarial hepatitis is centrizonal necrosis.[9,10] However, we came across this in only 1 patient. Four out of 5 of our patients showed reticuloendothelial cell hyperplasia and deposition of brown 'malarial pigment'. Although moderately severe abnormalities of liver function were present, only non-specific histological abnormalities were seen. This is similar to the findings in a report from north India, with the exception of fatty change which we did not encounter.[8] Organ damage in falciparum malaria is said to be related to the cytoadherence of parasitised red blood cells to the vascular and sinusoidal endothelium leading to 'stagnant anoxaemia'.[14] However, we were able to demonstrate parasites in the sinusoidal red blood cells in only 2 patients.

Liver function and structure abnormalities have also been described in severe systemic infections and endotoxaemia.[15,16] Endotoxaemia, without any evidence of bacterial infection, has been recorded in patients with complicated falciparum malaria[17] and may play a major role in causing hepatocellular jaundice and non-specific histological changes. However, patients with septicaemia often show marked cholestasis and may show mid-zonal or peripheral necrosis.[15,16] None of our patients showed these changes.

Our experience of 18 patients with malarial hepatitis suggests that it is a heterogenous entity with at least 2 clinical subsets. The mild form is widely recognized. However, the severe disease has clinical features similar to fulminant hepatic necrosis but is eminently treatable with anti-malarial drugs.

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