Clinical profile and complication of malaria hepatopathy

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Received 17 October 2012; received in revised form 3 March 2013; accepted 5 April 2013

KEYWORDS
Malaria;
Malarial hepatopathy;
Malarial hepatitis;
Liver function tests;
Plasmodium falciparum

Summary
Background: This study was designed to study the patient characteristics, presenting features and complications of malaria in patients with elevated liver enzymes and to compare these data to those of patients with normal liver enzymes.
Methods: A convenient sample of 100 patients with malaria was selected from three tertiary care referral hospitals. Study subjects were divided into two groups: (1) patients (controls) with normal liver enzymes and (2) patients (cases) with >3 times the normal liver enzymes in the absence of an alternate explanation for such elevation. Patient characteristics, presenting features and complications of malaria in these two groups were studied. Data were collected using a semi-structured pretested proforma and were analyzed using the statistical analysis program SPSS, version 11.5 (SPSS, Inc., Chicago, IL).
Results: The mean ages were 38.12 years for the cases and 35.20 years for the controls with a non-significant $p$ value of 0.289. Males composed 82% of the cases that were diagnosed with malarial hepatopathy; the remaining 18% were females. Falciparum malaria was present in 56% of the cases, compared to 12% of the controls.

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Introduction

Malaria is endemic in over 91 countries, setting at risk approximately 40% of the world population [1]. The disease accounts for 500 million clinical cases and more than a million deaths per year [2]; it is a major public health problem in developing countries and inflicts a huge health care burden in terms of morbidity and mortality [3–5].

Malarial hepatitis is characterized by hyperbilirubinemia (>3 mg/dl) and elevated transaminase enzymes of up to more than 3 times the normal levels [6]. Adherence of parasitized erythrocytes to the endothelial walls of liver capillaries leads to the blockade of intrahepatic channels, causing alterations in blood flow and, consequently, ischemia. As a result, complications such as hepatic encephalopathy, multiorgan failure and impaired protein synthesis occur. Histopathological studies have revealed hepatocyte necrosis, cholestasis, granulomatous lesions and malarial nodules [7].

According to the World Health Organization, signs of malarial hepatopathy are unusual in cases of malaria [8]. However, in recent years, signs of liver involvement have been increasingly reported in Asian countries, especially India, with a majority of cases suffering from falciparum malaria or mixed (both falciparum and vivax) malaria [8]. Cases with altered liver function tests and even fulminant hepatic failure have been reported [9,10]. A study conducted on Nigerian children concluded that the increased levels of liver enzymes are biochemical features of Plasmodium falciparum parasitemia [11]. However, the data on malarial hepatopathy is still sparse in the literature. This study was designed to evaluate the patient characteristics, presenting features and complications of malaria in patients with elevated liver enzymes and to compare these characteristics to those of patients with normal liver enzymes.

Materials and methods

This study was performed in three tertiary care referral hospitals in Mangalore, a malaria endemic coastal city in South India. These hospitals cater to a large number of patients with malaria. Adult patients presenting with fever who tested positive for malaria in a peripheral smear were enrolled in the study.

Inclusion criteria:

(1) The first group (controls) of patients included those suffering from malaria but who had normal liver enzymes.

(2) The second group (cases) included those patients who had elevated liver enzymes (>3 times the normal levels) due to malaria.

Exclusion criteria:

(1) Patients suffering from malaria and viral hepatitis A, B, C, D and E or viral hepatitis alone.

(2) Patients presenting with increased liver enzymes with conditions such as sepsis, drug-induced increase in liver enzymes or other similar conditions.

(3) Alcoholics.

(4) Patients <20 years old.

A convenient sample of 100 patients was considered. Institutional Ethics Committee approval was obtained at the first author’s institute. Study subjects were divided into two groups as mentioned above under the inclusion criteria. They were
informed about the details of the study, and written informed consent was obtained. Hypoglycemia was defined in the study as fasting blood sugar (FBS) <70 mg/dl. Data were collected using a semi-structured pretested proforma and were analyzed using the statistical analysis program SPSS, version 11.5 (SPSS, Inc., Chicago, IL). p-Values of less than 0.05 were considered significant.

Results

Age

Patients of all age groups above 20 years were enrolled in the study, as mentioned in the inclusion criteria, with maximum ages of 64 amongst cases and 77 amongst controls. The mean ages were 38.12 years in the cases and 35.20 years in the controls, with a non-significant p value of 0.289.

Sex

Males composed 82% of the cases that were diagnosed with malarial hepatopathy; the remaining 18% were females. In contrast, 68% of the controls were males, compared to 32% females (p = 0.106). These statistics are illustrated in Fig. 1.

Comparison of the incidences of different types of malaria

As can be seen from Fig. 2, 56% of the cases had falciparum malaria, compared to 12% of the controls. Additionally, 32% of the cases had vivax malaria, compared to 72% of the controls, and 12% of the cases had mixed malaria (due to both P. falciparum and P. vivax), compared to 16% of the controls. (p < 0.001).

Presenting complaints

In total, 100% of the study subjects in both the cases and the controls presented with fever with or without associated complaints. As can be seen in Fig. 3, 36% of cases had fever associated with chills, compared to 28% of the controls, 10% of each of the cases and controls had fever with body aches, 6% of cases had fever associated with headache, compared to 8% of the controls and 4% of cases had fever with vomiting, compared to 6% of the controls (Fig. 3).

Comparison of bilirubin

A total of 66% of cases of malarial hepatopathy presented with icterus, compared to 32% of the controls (Fig. 4). Out of these 66% of cases, 18.18%
Table 1  Incidence of thrombocytopenia in malaria subjects with and without hepatic involvement.

<table>
<thead>
<tr>
<th></th>
<th>Vivax malaria with thrombocytopenia</th>
<th>Falciparam malaria with thrombocytopenia</th>
<th>Mixed malaria with thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong></td>
<td>11</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td>26</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

19 cases (84.21%) suffering from hypoglycemia had falciparum malaria or mixed malaria.

**Correlation of thrombocytopenia with malarial hepatopathy**

Out of the 50 subjects in each group, 42 (84%) of the cases presented with thrombocytopenia, compared to 35 (70%) of the controls \((p<0.001)\) (Table 1). The mean platelet counts were 73,269.60 ± 38,720.87350 for the cases and 112,300.00 ± 65,178.32681 for the controls.

**Correlation of renal failure to malarial hepatopathy**

A total of 12% of the cases (6 out of 50) suffered from renal failure with serum creatinine levels >2 mg%, compared to 2% of the controls \((p = 0.060)\). This is shown in Fig. 6.

**Correlation of treatment received to patients with malarial hepatopathy**

Patients received oral chloroquine and primaquine, oral artesunate or intravenous artesunate based on malaria type and disease severity. In general, only 22% of patients with malarial hepatopathy...
received oral drugs, compared to 80% of the controls ($p < 0.001$). As seen in Table 2, 10% of the 22% of the cases taking oral therapy were on oral chloroquine and primaquine, and the rest (12%) were on oral artesunate. Of the controls, 46% out of the 80% who were taking oral therapy were on oral chloroquine and primaquine, and the rest (34%) were on oral artesunate. Intravenous artesunate was given to 78% of the cases, compared to only 20% of the controls (Fig. 7).

Discussion

In this study, adults of all age groups were affected by malaria. The most common age group involved was 21–30 years. A similar age incidence was noted by Muddaiah et al. in 2006 [12]. Cases and controls were predominantly male, which made up 82% and 68% of the group populations, respectively, versus 18% and 32% females. Previous studies conducted in South Canara, South India and Punjab, North India had concluded that males outnumbered females for reasons that remain unclear [12,13]. In the present study, the majority of patients with malarial hepatopathy suffered from falciparum and mixed infections. Although *P. vivax* is the major parasite type that causes malaria, most malaria complications are due to *P. falciparum* [12]. In a study conducted in North India [13], it was concluded that hepatic involvement was a common accompaniment of acute falciparum malaria, which is in accord with our study, the results of which indicated that *P. falciparum* (either causing infection by itself or along with *P. vivax*) was the most common species of *Plasmodium* that caused a three-fold rise in liver transaminase levels.

This study suggested a very significant correlation between elevated bilirubin levels and malarial hepatopathy. Among the cases, 66% of subjects presented with icterus, compared to only 32% of the subjects among the controls ($p = 0.003$). This finding is in accord with a study by Kausar et al. [14], which also established positive correlations between liver enzymes and bilirubin levels. In a study conducted in the United Arab Emirates from 2005 to 2007, it was concluded that hepatic dysfunction in acute falciparum malaria ranged from mild elevations of liver enzymes to acute hepatitis (alanine aminotransferase [ALT] >10 times the normal level). A significant finding in that study indicated that 87.5% patients with conjugated bilirubin levels greater than 3 mg/dl had increased ALT levels; in contrast, 45% patients with conjugated bilirubin levels less than 3 mg/dl had increased ALT levels, suggesting a positive correlation between bilirubin and increasing liver enzyme levels [15]. Liver function tests should be performed along with early diagnosis of *P. falciparum* malarial infections to ensure the early diagnosis of malarial hepatopathy.

The present study also established a very significant correlation between hypoglycemia and malarial hepatopathy ($p < 0.001$). Of the cases, 38% suffered from hypoglycemia with a fasting blood sugar <70 mg/dl, compared to 0% of the controls. Of these patients, 84.21% suffered from falciparum malaria. Hence, patients with malarial hepatopathy, especially with *P. falciparum* infection, have an increased chance of developing hypoglycemia. Studies conducted in Dakar [16] and Mali [17] have shown that hypoglycemia in severe malaria is a poor prognostic factor, with increased mortality rates in such cases.

Similarly, a significant correlation was observed between thrombocytopenia and malarial hepatopathy. Of the patients with malarial hepatopathy, 84% had thrombocytopenia in our study, compared to only 70% of the controls ($p < 0.001$). One study conducted in North India [10] that compared

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**Table 2** Group-wise distribution of the treatment received by the case and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Oral chloroquine and primaquine (%)</th>
<th>Oral artesunate (%)</th>
<th>Intravenous artesunate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases ($n = 50$)</td>
<td>10</td>
<td>12</td>
<td>78</td>
</tr>
<tr>
<td>Controls ($n = 50$)</td>
<td>46</td>
<td>34</td>
<td>20</td>
</tr>
</tbody>
</table>
thrombocytopenia to serum bilirubin established that the incidence of thrombocytopenia in patients with serum bilirubin >10 mg% was found to be higher than in patients with bilirubin levels <3 mg%.

There was no significant correlation between acute renal failure and malarial hepatopathy \( (p = 0.06) \).

Most of the patients with malarial hepatopathy were put on intravenous artesunate or oral artesunate, depending on disease severity. This approach is based on data suggesting that artesunate is superior to intravenous quinine for the treatment of adults with severe malaria in Asia \[18\].

Our study had a few limitations. First, the sample size was relatively small, involving only 100 patients. Second, the subjects were not followed up for the possible chronicity of their liver disease. Similarly, we did not analyze the time trend for the resolution of hepatopathy since the initiation of therapy. Additionally, the correlation between parasite burden and severity of hepatopathy was not analyzed. However, it is difficult to imagine a composite research study focusing on the rare incidence of malarial hepatopathy, and we have attempted to associate the complications likely to be present in malarial infections to the increased liver enzyme levels in the patients.

**Author's contribution**

AF, PVV and DG were involved in data collection and statistical analysis and drafted the first version of the manuscript. SP, SS, NA, AP and RGM conceived the study, reviewed the literature, interpreted the findings and critically revised the manuscript for intellectual content. AF, PVV and DG made equal contributions. All of the authors read and approved the final version of the manuscript.

**Conflict of interest statement**

**Funding:** No funding sources.  
**Competing interests:** None declared.  
**Ethical approval:** Declared.

**References**


