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ORIGINAL ARTICLE

A Prospective Study Of Hepatic Involvement In Plasmodium Falciparum Malaria

SINGH R*, KAUR M**, ARORA D***

ABSTRACT

Introduction: Malaria counts among the worst scourges of humankind. It amounts to an immeasurable health burden and inhibits economic prosperity in numerous tropical countries.

Material & Methods: The study included adult patients with Plasmodium Falciparum malaria with evidence of jaundice conventional thick and thin Pbfs stained with geimsa were examined under oil immersion. Detailed clinical, biochemical, and radiological examinations were conducted to establish the diagnosis of malaria and the various clinical manifestations. Histopathological examination was conducted in the category B of the patients.

Observations: About two thirds were male. The age of the patients ranged between 16-56 years (mean 28.14±7.23). Serum bilirubin levels ranged from 1 to 32 mg% (mean 5.65). 41.46% had serum bilirubin of <3 mg%, 40.24% had 3-10 mg% and 18.29% had >10 mg%.

The most frequent sonographic finding of liver was normal sized liver with normal echogenicity. Swollen hepatocytes was seen in all the cases while hemozoin deposition seen in about three fourths.80% of the patients with serum bilirubin >10mg developed acute renal failure as compared to 17.65% in those with bilirubin level <3 mg.

Conclusion: Hepatic involvement is a common accompaniment of acute P. Falciparum malaria, and hepatic dysfunction ranges from a mild elevation of liver enzymes to the range of acute hepatitis.the presence of hepatitis in patients with falciparum malaria indicates a more severe illness with a higher incidence of complications, multiorgan failure and supposedly a bad prognosis.

Key Words: P. Falciparum, Malaria, malarial hepatitis, Swollen hepatocytes, Hemozoin deposition

*(Asst.Prof.), Department of Internal Medicine, (Asst. Prof),Department of Radiodiagnosis, (Asst.Prof.) Department of Microbiology, Adesh Institute of Medical Sciences & Research. Bhatinda, Punjab, -151001 (India).

Corresponding Author
Dr. Rakendra Singh (Asst. Prof.)
Department of Internal Medicine, Adesh Institute of Medical Sciences & Research.Bathinda, Punjab, India-151001.
E-mail: rakendrasingh@hotmail.com
TEL NO: +919815409999 / +919779109999
FAX NO: +911642742902

Introduction

Malaria is an ancient disease and references to what was almost certainly malaria occur in a Chinese document from about 2700 BC, clay tablets from Mesopotamia from 2000 BC, Egyptian papyri from 1570 BC and Hindu texts as far back as the sixth century BC. Malaria counts among the worst scourges of humankind, accounting for some 500 million clinical cases per year and more than one million deaths, mostly children [1]. It amounts to an immeasurable health burden and inhibits economic prosperity in numerous tropical countries, most extensively in Africa & Asia. *Plasmodium falciparum* is the most

virulent among the four *Plasmodium* species parasitic to humans, accounting for about 85% of all malaria cases, and nearly all of the mortality. The extreme pathogenicity of *P. falciparum* has suggested that it is a recent human parasite, acquired by transfer from a nonhuman host [2].

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 [3]. 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, including India more so in recent years [4],[5]. The majority of the cases have either isolated infection with *P. falciparum* or a mixed infection with both *P. falciparum* and *P. vivax* [6],[7].Malarial hepatitis is a term commonly used to describe hepatocyte dysfunction in severe and complicated malaria [8]. 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 [9].

Hence malarial hepatitis is a component of multiorgan failure and supposedly a bad prognostic sign in Falciparum Malaria. So, the present study was designed to determine the clinical, biochemical and sonographic changes in patients with falciparum malaria presenting with jaundice and thus prognosticate the disease.

Materials And Methods

This prospective study was conducted on 82 admitted adult patients in the medicine ward of Adesh Institute of Medical Sciences & Research, a 750 bedded teaching hospital in North India. The time period of the study was from July 2006 through December 2009. Detailed clinical, biochemical, and radiological examinations were conducted to establish the diagnosis of malaria and the various clinical manifestations. Histopathological examination was conducted in the category B of the patients.(those in the middle group.)

Selection Criteria

It included adult patients of both sexes and different ages with Plasmodium falciparum malaria with evidence of jaundice after obtaining the formal consent from the patient or relatives.

Exclusion Criteria

Patients who had other concurrent illness or having negative peripheral blood smear for PF (or having only vivax infection) were not included in the study.

The study was designed to include the Demographic, clinical information, biochemical and hematological changes observed in the patients. The data was entered into a structured proforma separately. Management was done as per standard guidelines. Patients were discharged from the hospital after significant improvement in clinical as well as hematological and biochemical parameters.
Any patient with evidence of liver disease (e.g. viral hepatitis, cirrhosis, portal hypertension, liver abscess, unexplained hepatomegaly, ascites, history of alcoholism/ 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 these patients of *Plasmodium falciparum* malaria with jaundice were evaluated clinically for history of fever, headache, vomiting, altered sensorium, convulsions, pallor, icterus, hepatosplenomegaly, decreased urine output and coma.

A total of 82 patients conformed to the selection criteria and were included as a part of the sample size. The diagnosis of malaria was confirmed by the demonstration of asexual forms of *Plasmodium falciparum* in the peripheral smear alongwith jaundice. Conventional thick and thin PBFs stained with Geimsa were examined under oil immersion. Slides were considered negative when there were no parasites in 100 high power fields.

The laboratory investigations done in all the patients included a complete hemogram, ESR, platelet count, BT, CT, random blood sugar, urea, creatinine and S. electrolytes. Liver function was evaluated by determining the levels of S. bilirubin (both conjugated and unconjugated), AST and ALT, S. protein, and prothrombin time (PTI). Blood for hepatitis B and C was done in all the patients to rule out possibility of concomitant viral hepatitis. Urine was evaluated for urobilinogen, bile pigment and bile salts.

Based on serum bilirubin level, the patients were categorized in group A (serum bilirubin < 3mg %), group B (serum bilirubin 3-10 mg %) and in group C (serum bilirubin >10 mg %).

Detailed ultrasonography was done to check the size and echo texture 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 *falciparum* infection, at least three-fold rise in transaminases (especially ALT, demonstrated in two samples, taken 24 hours apart,) absence of clinical or serological evidence of viral hepatitis and response to anti-malarial therapy [12].

Liver biopsy was done by gun shot method through micro invasive needle using transthoracic approach in ninth or tenth intercostal space in the mid-axillary line in all the thirty three patients of group B after obtaining reports of BT, CT, PT, platelet count and patients consent. The formalin fixed liver tissue was stained with hematoxylin and eosin, periodic acid Schiff's and reticulin stains.

Formal approval of hospital ethical committee and written consent of the patients were obtained for this study.

Observations

A total of 82 patients fulfilled the inclusion criteria, 56 (68.29%) were males and 26 (31.71%) females. The age of the patients ranged between 16-56 years (mean 28.14±7.23). The most common presenting symptoms were high-grade fever with chills & rigors along with vomiting followed by abdominal pain, headache & impaired consciousness. The average duration of illness was 1-8 days before the patients presented to the hospital.

The important findings were icterus in all the patients, pallor in 53 (64.63%), splenomegaly in 42 (51.22%), hepatomegaly in 48 (58.54%) and impaired consciousness in 17 (20.73%) cases. The details of biochemical investigations are mentioned in the [Table/Fig 1]. Serum bilirubin levels ranged from 1 to 32 mg% with mean bilirubin level of 5.65±2.64 mg/dl. 34 patients (41.46%) had serum bilirubin of <3 mg%, 33 (40.24%) had 3-10 mg% and 15 (18.29%) had >10 mg%.

(Table/Fig 1) Demographic, Clinical, Biochemical & Hematological Parameters

Parameters	No. of patients (%age)		
Clinical Category	A (Bil < 3)	B (Bil= 3 - 10)	C (Bil > 10)
Male	24	21	11
Female	10	12	4
Fever	30	31	12
Pallor	22	16	9
Impaired Consciousness	2	5	10
Hepatomegaly	8	28	12
Splenomegaly	12	17	13
Raised ALT > 3 times	2	4	5
Anemia (Hb <9)	18	27	13
Thrombocytopenia	4	8	10
Increased ser. creatinine	6	14	12
Death	0	2	5

ALT (alanine transaminases) levels ranged from 32-1240 IU/L with mean ALT levels 78.62±41U/L. AST (Aspartate transaminases) levels ranged from 28- 1460 IU/L with a mean of 62.48±32.24. In 11 patients (13.41%), serum transaminase levels were more than thrice the upper limit of normal. Prothrombin time was within normal limits in most patients except a few with severe malaria with very high serum bilirubin levels. Prothrombin time index (INR) ranged from 1-2.3 with a mean level of 1.4. Anemia was found in 58 (70.73%) patients with mean Hb% 9.85±3 gm/dl. 22 (26.83%) patients had evidence of thrombocytopenia with mean platelet count 2.36±59.28x10^3 cells/ul. Only 2 (2.44%) patients had leucocytosis. Creatinine was increased in 32 (39.02%) patients with mean serum creatinine level of 1.8±0.8 mg/dl. 7 (8.54%) patients died due to various complications of malaria like cerebral malaria or multi-organ dysfunction.

The most frequent sonographic finding of liver was normal sized liver with normal echogenicity (36.59%) followed closely by hepatomegaly with normal echogenicity (34.15%) [Table/Fig 2]. 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/Fig 2) Sonographic Findings.

USG findings	No. of patients n=82	%age
Normal size with normal echogenicity of liver	30	36.59
Normal size with decreased echogenicity of liver	4	4.88
Hepatomegaly with normal echogenicity of liver	28	34.15
Hepatomegaly with decreased echogenicity of liver	20	24.39
Increased wall thickness of gall bladder	11	13.41
Splenomegaly	42	51.22
Ascites	6	7.32

The important histopathological features were the presence of swollen hepatocytes in 33 (100%) cases, presence of malarial pigment (hemozoin) deposition in 24 (72.73%) cases, portal infiltration by mononuclear cells in 18 (54.55%), congestion of hepatocytes in 15 (45.45%), Kupffer cell hyperplasia in 10 (30.30%), centrizonal necrosis in 8 (24.24%) and fatty infiltration in 4 (12.12%) of cases [Table/Fig 3].

(Table/Fig 3) Changes In Histopathology In Liver In Patients Of Plasmodium Falciparum Malaria With Jaundice

Changes in Histopathology	No. of Patients (N = 33)	% age
Swollen hepatocytes	33	100
Pigment deposition	24	72.73
Portal infiltration	18	54.55
Sinusoidal infiltration and dilatation / congestion	15	45.45
Kupffer cell hyperplasia	10	30.30
Liver cell necrosis	8	24.24
Fatty change	4	12.12

Discussion

Hepatic dysfunction in a case of falciparum infection has been recognized since the beginning and various causes have been attributed for the same. According to WHO, the jaundice is one of the important manifestations of severe malaria. There is evidence of focal hepatocyte necrosis, cholestasis, bile stasis, granulomatous lesion or malarial nodules [18].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). The other causes of jaundice in malaria could be coexistent viral hepatitis, especially infections with hepatitis E virus or hepatitis A virus [16].

Many studies have attributed malarial hepatitis to be an important contributory factor for the jaundice [5], [12], [23]. Malarial hepatitis is a term commonly used to describe liver cell dysfunction in severe and complicated malaria. Malarial hepatitis is characterized by a rise in serum bilirubin along with the rise in serum Alanine

transaminase levels to more than three times the upper limit of normal [4]. The incidence of jaundice and hepatocellular dysfunctions in severe malarial infection has 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 [8]. The incidence of jaundice is more in adults [3] and it varies from 32-37% with predominant unconjugated hyperbilirubinemia as reported by Harris *at al.* (10) In patients with severe malarial infection, the incidence of jaundice is reported to be 2-57% [11].

Kochar *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 [14]. The findings of our study are consistent with the above study as we also noted dominant conjugated hyperbilirubinemia in those patients who had deranged LFTs and in 13.42% of the patients, ALT was >3 times of normal level.

Many workers have proposed the role of hepatocellular damage in patients having hyperbilirubinemia of greater magnitude [19],[20].According to WHO, the patients of severe falciparum malaria with jaundice rarely have the serum bilirubin levels of more than 10mg%[18] but in our study 18.29% patients had serum bilirubin levels of >10mg% and the maximum value was 32 mg%. Earlier similar findings were recorded by many workers from this subcontinent [4],[21]. The reason for this could be due to endemicity of malaria in our part of the world and more drug resistant virulent strains. Moreover, haemolysis alone can produce predominantly unconjugated hyperbilirubinemia which usually does not exceed more then 10 mg%. In patients having serum bilirubin levels of more then 10 mg%, there are more chances of associated hepatocellular injury as compared to the patients having serum bilirubin levels of less then 10 mg%.

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 our study, out of the patients with serum bilirubin >10mg, 80% developed acute renal compromise as compared to 42.42% with bilirubin level between 3-10 and, 17.65% in those with bilirubin level <3 mg. Higher mortality rate was observed (33.33% vs. 6.06%) in category C compared with category B, while there was no mortality in category A. Similar observations have been reported by other studies [4]. In a study on severe FM presenting as multi-organ failure, multiple organ involvement was associated with increased mortality and hepatic failure was associated with around 50% mortality rate [22]. Similar reports have been published by others [23].

It has also been observed that higher serum bilirubin levels are associated with increased incidents of complications and mortality [12]. In this study we also observed raised serum enzyme levels in some of these patients and 9 out of 12 patients having serum bilirubin levels of more then 10mg% also had very high levels of serum enzymes. Earlier Chawla *et al* and Anand *et al* also had similar observation in the patients of PF malaria [4],[21] All these observations of this study and other workers further support the possible role of hepatic dysfunction in the causation of jaundice.

We noted a higher incidence of thrombocytopenia (66.67% vs 11.76%) and anemia (86.67% vs. 52.94%) in patients with category C compared with category A. Similar reports of thrombocytopenia due to *P.falciparum* malaria were also documented by Kochar *et al.* and other studies [14],[15]. We document a couple of patients with markedly elevated Prothrombin time. These patients however fall into category C that is, these patients had severe *P.falciparum* malaria and significant disturbance was

observed in the coagulation profile. However 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 [11].

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 [17]. Bilirubin normally recedes by 72 hours of starting treatment but it may be delayed in patients having coexisting renal dysfunction. 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.

The predominant histopathological changes in malarial liver comprises of a reticulo endothelial response i.e., Kupffer cell hyperplasia, presence of malarial pigment and congestion alongwith minor effects on hepatocytes [21],[22],[23] Malarial parasites are not found in the biopsy specimens [24]. These changes may be non-specific but the presence of centrizonal necrosis and hyperplastic Kupffer cells loaded with malarial pigment is a strong indicator of hepatic damage [25] .

Thus, in our opinion the evidence of predominantly conjugated hyperbilirubinemia and increased levels of ALT, AST and LDH levels along with evidence of hepatocllular necrosis in histopathological examination in few patients are evidence of hepatocytic dysfunction in patients of *Plasmodium falciparum* malaria with jaundice.

Regarding liver function tests, the maximum value of serum bilirubin observed in this study was 32 mg% while in a study done by Kocher *et al.,* it was 48mg% [14]. Highest level of ALT and AST was 1240 IU/L and 1460 IU/L respectively while in Kocher *et al's* study, it was 1120 IU/L and 1245 IU/L respectively. Chawla *et al.* studied 31 patients, of whom 14 (45.16%) had serum bilirubin >10 mg%, with predominantly conjugated hyperbilirubinemia. [21] 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 [4]. 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 [6].

In this study, the most common sonographic finding was normal size and normal echogenic liver followed closely by hepatomegaly and normal echogenicity of liver. Similarly Hepatomegaly and normal prothrombin time in the setting of FHF are suggestive of malaria. [25]. Although the authors mentioned that hepatomegaly is associated with MHsFHF, it appears that splenomegaly is similarly associated (48% in patients with MHsFHF vs none in the viral FHF group) [11], [26]. 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 features of widespread hepatocyte dysfunction.

Conclusion

Hence we conclude that hepatic involvement is a common accompaniment of acute *P. falciparum* malaria, and hepatic dysfunction ranges from a mild elevation of liver enzymes to the range of acute hepatitis. Malarial hepatopathy is a well recognized entity which can be reliably diagnosed on the basis of clinical, biochemical and sonographic parameters and should be suspected in patients with acute febrile illness, jaundice and raised transaminases

and there is no role for histopathology. Furthermore, it was also noted that hepatic dysfunction with jaundice is a serious development in acute *P.falciparum* malaria and it indicates severe illness with higher incidence of complication and mortality. To help mitigate the expanding global impact of malaria, with its associated increasing drug resistance, implementation of prompt and accurate diagnosis is needed. Numerous malaria RDTs have been developed and are widely available; however, an assortment of issues related to these products have become apparent [27],[28]

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