J Vect Borne Dis 43, September 2006, pp. 123–129

A comparative study of regression of jaundice in patients of malaria and acute viral hepatitis

D.K. Kochar[a], K. Kaswan[a], S.K. Kochar[a], P. Sirohi[a], M. Pal[a], A. Kochar[a], R.P. Agrawal[a] & A. Das[b]

[a]*Department of Medicine, S.P. Medical College, Bikaner, India;* [b]*Birla Institute of Science & Technology, Pilani, India*

Abstract

Background & objectives: Jaundice is one of the common manifestations of severe malaria in adults. The purpose of this study is to compare the pattern of clinical and biochemical parameters such as serum bilirubin and liver enzyme levels in patients of malaria with jaundice and acute viral hepatitis.

Methodology: The present study was conducted on 34 patients of malaria with jaundice and 15 patients of acute viral hepatitis. Estimation of serum bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT) and alkaline phosphatase was done daily using standard procedures in malaria patients and weekly in acute viral hepatitis patients.

Results: Mean level of serum bilirubin on first day in malaria and acute viral hepatitis patients was 7.07 ± 3.94 and 10.38 ± 7.87 mg%, whereas on Day 8 it was 1.19 ± 1.43 and 7.88 ± 7.02 mg% respectively. Mean level of AST on Day 1 in malaria and acute viral hepatitis patients was 158.47 ± 120.35 and 1418.6 ± 834.11 IU/L, whereas on Day 8 it was 41 ± 28.33 and 775.3 ± 399.01 IU/L respectively. Mean level of ALT on Day 1 in malaria and acute viral hepatitis patients was 220.14 ± 145.61 and 1666.67 ± 1112.77 IU/L, whereas on Day 8 it was 50.85 ± 37.31 and 823.8 ± 475.06 IU/L respectively. Mean level of serum alkaline phosphatase on Day 1 in malaria and acute viral hepatitis patients was 394.74 ± 267.78 and 513.4 ± 324.7 IU/L, whereas on Day 8 it was 84.76 ± 68.50 and 369.27 ± 207.75 IU/L respectively.

Interpretation & conclusion: We observed that resolution of jaundice in malaria took 1–2 weeks in contrast 6 to 8 weeks in viral hepatitis. This difference in duration was statistically significant. Thus, jaundice not resolving in 1–2 weeks time in a patient of malaria requires serious consideration for presence of other concomitant diseases including viral hepatitis.

Key words ALT – AST – jaundice – malaria – viral hepatitis

Introduction

Malaria is endemic in more than 100 countries, affecting 300–500 million people and is causing 1.0–2.5 million deaths annually. It is endemic in tropical and subtropical countries affecting 40% of world's population living in these areas[1]. Jaundice is one of the common manifestations of severe malaria in adults and its incidence vary from 10–45% in different regions. Over a decade ago, cerebral malaria was

the predominant manifestation of severe malaria, whereas today the combination of hepatic dysfunction and renal failure is observed more commonly[1]. A study from Vietnam reported that 63% of adult patients of malaria having acute renal failure also had jaundice[2]. Presence of jaundice in malaria indicates more severe illness with higher incidence of complication and the mortality rate was also higher in this group of patients (40 *vs* 17%)[3].

According to WHO, apart from jaundice signs of hepatic dysfunction are unusual and clinical signs of liver failure such as asterexis or liver flaps are never seen unless there is concomitant viral hepatitis[1]. However, in recent years many reports with definite evidence of hepatic encephalopathy have been reported from different parts of the world, including India[4-8]. Recovery from jaundice in malaria is usually faster than acute viral hepatitis, where it takes longer time to return to normal.

The purpose of this study is to compare the pattern of clinical and biochemical parameters and their course in patients of malaria with jaundice and acute viral hepatitis.

Material & Methods

Study subjects: This was a prospective study done from July 2004 to November 2004 on consecutively admitted patients in classified malaria ward of Prince Bijay Memorial (PBM) Hospital, Bikaner and patients of acute viral hepatitis attending Gastroenterology OPD. The study involved 47 adults both male and female of all socioeconomic groups and from both rural and urban areas diagnosed as malaria with jaundice (Group A) and 25 patients were of acute viral hepatitis (Group B).

Inclusion and exclusion criteria: The diagnosis of malaria was done according to WHO criteria by demonstration of asexual phase of malaria parasite in peripheral blood film (PBF)[1]. Only patients having serum bilirubin more than 3 mg% were included in the study. Patients of acute viral hepatitis were diagnosed by clinical and biochemical parameters and confirmed by viral markers. Patients taking any drug causing hepatotoxicity or ayurvedic medicine and alcohol for long duration or having concomitant renal failure were excluded from the study. In group A, 14 patients were excluded as 3 were chronic alcoholic, 2 were taking antitubercular drugs, 6 patients were taking ayurvedic medicine, 3 had concomitant renal failure. In group B, 10 patients were excluded as 2 were chronic alcoholic, 5 patients were taking ayurvedic medicine before admission, one patient was on antitubercular drugs and 2 patients developed hepatic encephalopathy.

Investigations: Serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase were determined in all the patients on Day 1 and then daily for next seven days. Blood examination for haemoglobin (Hb), total leukocyte count (TLC), differential leukocyte count (DLC), platelet count, erythrocyte sedimentation rate (ESR), blood sugar, blood urea, serum creatinine and ELISA for leptospirosis, viral markers for viral hepatitis and urine for complete and microscopic examination were done in all patients. CT scan brain, lumbar puncture and cerebro spinal fluid (CSF) analysis were done in all doubtful cases to rule out meningitis and encephalitis, specially in cases of cerebral malaria. Acute viral hepatitis was diagnosed by history, clinical features and laboratory investigations including S. bilirubin, AST, ALT, alkaline phosphatase and relevant viral markers including hepatitis B surface antigen (HBs Ag), anti hepatitis B core antibody (anti HBc Ab), anti hepatitis C virus antibody (anti HCV Ab) and IgM anti hepatitis A virus antibody (IgM anti HAV Ab). Liver function tests for acute viral hepatitis were done at the time of diagnosis and then at weekly interval for next 6 weeks. Ultrasonography was also done for each patient by using Shematzu Sonography Machine and 3.5 Hz (Phased array) probe was used and done in

2D grey scale, real time mode. The day of diagnosis of the patient was considered as first day for all investigations.

Treatment: All the patients of malaria were treated with i.v. quinine 10 mg/kg 8 hourly until a patient started tolerating orally up to the time of 7 days in addition to symptomatic treatment, whereas patients of acute viral hepatitis were treated with rest and symptomatic treatment on the outdoor basis.

Results

All the 34 patients of malaria with jaundice (Group A) were having *Plasmodium falciparum* infection. Mean level of S. bilirubin on the first day in malaria and acute viral hepatitis was 7.07 ± 3.94 and 10.38 ± 7.87 mg%, whereas on Day 8 it was 1.19 ± 1.43 and 7.88 ± 7.02 mg% respectively. Mean regression of bilirubin in malaria with jaundice was 5.87 mg% and in viral hepatitis it was 2.50 mg%. The inter group regression pattern of bilirubin was statistically significant ($p < 0.0002$). Most of the patients of malaria and acute viral hepatitis in this study had S. bilirubin in the range of 5–10 mg%. About 14.7% cases of malaria with jaundice and 33% cases of acute viral hepatitis had their initial S. bilirubin level >10 mg% as shown in Table 1. We also observed that patients of both the groups had predominant conjugated type hyperbilirubinemia. On Day 8 of treatment the patients of malaria with jaundice had almost normal level of S. bilirubin, AST, ALT and alkaline phosphatase but patients of acute viral hepatitis had higher level as shown in Table 2 and Fig. 1.

The mean level of AST on first day was 158.47 ± 120.35 and 1418.6 ± 834.11 IU/L in patients of ma-

Table 1. Levels of S. bilirubin and liver enzymes in patients of malaria with jaundice and acute viral hepatitis

Parameter	Group A (n=34)	Group B (n=15)	χ^2 value	p-value
S. bilirubin level				
< 5 mg%	13 (38.24%)	2 (13.33%)	1.979	NS
5–10 mg%	16 (47.06%)	8 (53.33%)	0.009	NS
>10 mg%	5 (14.71%)	5 (33.33%)	1.224	NS
AST level				
<100 IU/L	13 (38.24%)	Nil	5.96	<0.05
100–200 IU/L	13 (38.24%)	Nil	5.96	<0.05
>200 IU/L	8 (23.53%)	15 (100%)	21.463	<0.001
ALT level				
<100 IU/L	4 (11.76%)	Nil	0.672	NS
100–200 IU/L	16 (47.06%)	Nil	8.450	<0.01
>200 IU/L	14 (41.18%)	15 (100%)	12.573	<0.001
S. alkaline phosphatase				
<200 IU/L	5 (14.71%)	1 (6.67%)	0.101	NS
200–600 IU/L	23 (67.65%)	11 (73.33%)	0.003	NS
>600 IU/L	6 (17.65%)	3 (20.00%)	0.041	NS

NS — Non-significant.

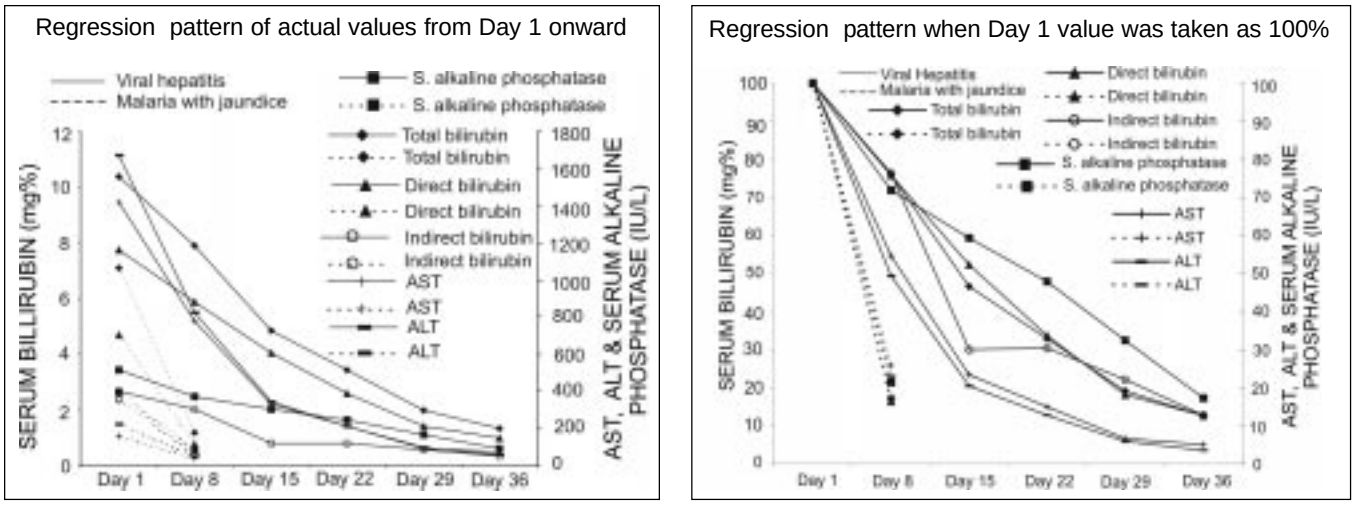

Fig. 1: Regression pattern of the serum bilirubin and liver enzymes in the patients of malaria with jaundice and acute viral hepatitis

laria and acute viral hepatitis, whereas on Day 8 it was 41 ± 28.33 and 775.3 ± 399.01 IU/L respectively (Table 2). AST level of < 200 IU was found in 76% patients of malaria, whereas not in a single patient of acute viral hepatitis and level of >200 IU was consistently present in patients of acute viral hepatitis. Similarly, the ALT level of < 200 IU was found in 59% cases of malaria but not in a single patient of acute viral hepatitis. Although 41% patients of malaria also had ALT level of > 200 IU, the same in patients of acute viral hepatitis was significantly higher (Table 1). Mean level of ALT on first day was 220.14 ± 145.61 and 1666.67 ± 1112.71 IU/L in patients of malaria and acute viral hepatitis, while the same on Day 8 was 50.85 ± 37.31 and 823.8 ± 475.35 IU/L respectively. Serum alkaline phosphatase was in the range of 200–600 IU/L in most of the patients of both malaria and acute viral hepatitis (Table 1). Mean level of serum alkaline phosphatase on the first day was 394.73 ± 267.78 and 513.4 ± 324.7 IU/L in patients of malaria and acute viral hepatitis, while the same on Day 8 was 84.76 ± 68.50 and 369.76 ± 207.75 IU/L respectively. Comparison of the regression of the enzyme was statistically significant for serum alkaline phosphatase level. Mean regression of the bilirubin and liver enzyme in both the groups

Table 2. Mean value of S. bilirubin and liver enzymes on Day 1 and Day 8 in patients of malaria with jaundice and acute viral hepatitis

Parameter	Group	Day 1	Day 8	Percent regression (%)	t-value	p-value
S. bilirubin (mg%)	Group A	7.07 ± 3.94	1.19 ± 1.43	84.67	0.032	1.3
	Group B	10.38 ± 7.87	7.88 ± 7.02	26.44	–0.018	0.366
AST (IU/L)	Group A	158.47 ± 120.35	41 ± 28.33	67.62	0.663	5.68
	Group B	1418.6 ± 834.11	775.3 ± 399.01	39.26	3.989	0.011
ALT (IU/L)	Group A	220.14 ± 145.61	50.85 ± 37.31	73.56	0.956	9.46
	Group B	1666.67 ± 1112.77	823.8 ± 475.06	42.56	4.761	0.011
Alkaline phosphatase (IU/L)	Group A	394.74 ± 267.78	84.76 ± 68.50	77.26	1.750	1.06
	Group B	513.4 ± 324.7	369.27 ± 207.75	23.16	0.814	0.158

Table 3. Mean regression of bilirubin and liver enzyme levels at the end of one week

Parameter	Group A	Group B	p-value
Serum bilirubin (mg%)	5.87	2.5	0.0002
AST (IU/L)	117.47	643.26	1.53
ALT (IU/L)	169.29	842.86	6.81
Alkaline phosphatase (IU/L)	309.97	144.13	0.009

from Day 1 to 8 is shown in Table 3. The regression of the bilirubin and alkaline phosphatase was statistically significant, while regression of AST and ALT was statistically insignificant.

The detailed ultrasonographic study revealed that altered echopattern of liver and increased gall bladder wall thickness was more commonly observed in patients of acute viral hepatitis, in contrast, splenomegaly was more commonly seen in patients of malaria (71 *vs* 13%; Table 4).

We also studied the clearance pattern of serum bilirubin in patients of malaria with jaundice and compared it with patients of acute viral hepatitis. The result showed that S. bilirubin, AST, ALT and alkaline phosphatase levels return to normal at the end of first week in most of the patients of malaria with jaundice and in the next week in the remaining few. In contrast, the same changes in acute viral hepatitis took 6–8 weeks. On Day 8 we found significant reduction in S. bilirubin, AST, ALT and alkaline phosphatase levels in patients of malaria with jaundice as compared to the patients of acute viral hepatitis (Fig. 1).

Discussion

Intravascular haemolysis of parasitised and non-parasitised red blood cells have been considered as an important factor for causation of mild to moderate jaundice that is predominantly unconjugated. But the haemolysis as a sole factor may not be responsible for severe jaundice or conjugated hyperbilirubinemia along with increase in serum levels of liver enzymes (AST and ALT) seen in many patients of malaria. The role of liver injury or hepatocellular damage in these patients has been proposed by many workers specially in the Indian subcontinent[3,4,6,9,10]. Very high serum bilirubin level with predominant conjugated hyperbilirubinemia, along with increase in the liver enzymes are important denominator of liver injury in these patients.

In this study on 34 patients of malaria with jaundice, the level of total S. bilirubin was in the range of

Table 4. Ultrasonographic findings in patients of malaria with jaundice and acute viral hepatitis

USG findings	Group A (n=34)	Group B (n=15)	χ^2 value	p-value
Liver				
Size enlarged	16 (47.06%)	10 (66.67%)	0.9158	NS
Altered echo patterns	8 (23.53%)	6 (40%)	0.694	NS
Normal architecture	34 (100%)	15 (100%)		
Gall bladder				
Increased wall thickness	8 (23.53%)	8 (53.33%)	2.958	NS
Lumen, sludge	10 (29.41%)	6 (40%)	0.1583	NS
Clear lumen	24 (70.59%)	9 (60%)	0.1583	NS
Spleen enlargement	24 (70.59%)	2 (13.33%)	11.497	< 0.001

NS — Non-significant.

3–17.4 mg% (7.07 ± 3.94). Five patients (15%) had S. bilirubin of >10 mg%. The incidence of complications was also higher in patients with increased S. bilirubin level. In the patients of acute viral hepatitis, the S. bilirubin level was in the range of 2.3–31 mg% (10.38 ± 7.87). Five patients (33%) of acute viral hepatitis had S. bilirubin level of more than 10 mg%. Kochar *et al*[9] studied 86 patients of malarial hepatitis, out of those 29 cases had S. bilirubin level of more than 10 mg%. Maximum value of S. bilirubin was 48.2 mg%. These findings are in accordance with this study in patients of malaria with jaundice. We also observed that both groups of patients had predominant conjugated hyperbilirubinemia. Few studies carried out earlier have also observed predominant conjugated hyperbilirubinmia in patients of malarial hepatitis[3,4,6,9,10].

In patients having serum bilirubin >10 mg%, the hepatocellular injury should be an important causative factor in the pathogenesis of hyperbilirubinemia, as compared to patients having S. bilirubin <10 mg%, in which the haemolysis, disseminated intravascular coagulation (DIC) may be the only important factor. It has also been reported that hyperparasitaemia is associated with higher serum bilirubin level along with increased incidence of complications like anaemia, haemoglobinuria leading to blackwater fever, algid malaria and acute renal failure.

Many patients of malaria with jaundice had significantly higher levels of AST and ALT. In patients of acute viral hepatitis, AST and ALT were significantly increased, even more than 10 times of normal limit. We found that both patients of malaria with jaundice and acute viral hepatitis had linear increase in AST and ALT with increasing level of S. bilirubin. In patients of malaria with jaundice the AST and ALT levels were in the range of 36–510 and 48–678 IU/L respectively. Patients of acute viral hepatitis had marked increase in AST and ALT levels and they were in the range of 336–2880 and 402–3940 IU/L respectively. Similar findings having AST and ALT level in the range of 100–300 IU/L have been reported[10]. Whereas Anand *et al*[4] found AST and ALT in range of 256.8 ± 154.4 and 351.9 ± 239.4 IU respectively in malaria patients.

Kochar *et al*[11] observed that patients of malarial hepatitis had linear increase in AST and ALT levels with increasing bilirubin level. They observed that AST and ALT in patients with S. bilirubin less than 10 mg% were in the range of 163.11 ± 76.79 and 202.98 ± 120 IU/L respectively, whereas patients with S. bilirubin more than 10 mg% had AST and ALT levels in the range of 563.03 ± 303.13 and 669.83 ± 368.08 IU/L respectively. These observations are in accordance with the present study and indicate hepatocellular damage in these patients especially those having S. bilirubin > 10 mg%. In a recent study[12] it was reported that in 11 patients of complicated vivax malaria, 4 patients had jaundice and the highest levels of AST and ALT in these patients were 546 IU/L and 510 IU/L respectively.

We observed that both patients of malaria with jaundice and acute viral hepatitis had increased S. alkaline phosphatase. The range of S. alkaline phosphatase in patients of malaria with jaundice and acute viral hepatitis was 102–1121 and 180–1482 IU/L respectively. Increased level of S. alkaline phosphatase with predominant conjugated hyperbilirubinemia in patients of malaria with jaundice indicates cholestasis. Prothrombin time was also increased in some patients of malaria with jaundice. Hills[13] observed moderately prolonged prothrombin time in patients of malaria with jaundice and their observations are in accordance with the present study.

In this study we also observed that altered echo pattern and increased gall bladder wall thickness were present in both malaria and acute viral hepatitis patients. Splenomegaly was commonly associated finding in patients of malaria with jaundice as compared to acute viral hepatitis (71 *vs* 13%), as reported earlier by other workers[11,14,15].

The difference of S. bilirubin level on Day 1 and 8 in two groups was statistically highly significant. These changes indicate that S. bilirubin level comes to normal level in 1–2 weeks, in the patients of malaria with jaundice after appropriate treatment, whereas in patients with acute viral hepatitis it takes 6–8 weeks. Similar pattern was also observed in the levels of AST, ALT and alkaline phosphatase in malaria with jaundice as reported earlier by Kochar *et al*[11], who observed that patients of malarial hepatitis took 1–3 weeks for disappearance of jaundice. They also observed that patients with S. bilirubin < 10 mg% had complete disappearance of jaundice within 10 days, whereas those with initial S. bilirubin level of 10–20 mg% took about 15 days. These findings corroborate with our observation of a steep fall in the level of S. bilirubin in patients of malaria with jaundice after appropriate treatment. Thus, jaundice not resolving in 1–2 weeks time in a patient of malaria requires serious consideration for the presence of other concomitant diseases including viral hepatitis.

References

1. WHO. Severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2000; (Suppl 1): 1–90.

2. Trang TT, Phu NH, Vinh H, Hien TT, Cuong BM, Chau TT, Mai NT, Waller DJ, White NJ. Acute renal failure in patients with severe falciparum malaria. *Clin Inf Dis* 1992; *15:* 874–80

3. Murthy GL, Sahay RK, Sreenivas DV, Sundaram C, Shantaram V. Hepatitis in falciparum malaria. *Trop Gastroenterol* 1998; *19:* 152–4.

4. Anand AC, Ranji C, Narula AS, Singh W. Histopathological changes of liver in malaria: a heterogenous syndrome? *Natl Med J India* 1992; *5:* 59–62.

5. Mishra SK , Mohanty S, Das BS, Patnaik JK, Satpathy SK Mohanty D, Bose TK. Hepatic changes in *Plasmodium falciparum* malaria. *Indian J Malariol* 1992; *29:* 1167–71.

6. Ashan T, Rab SM, Sheekhani MS. Falciparum malaria or fulminant hepatic failure? *J Pak Med Assoc* 1993; *43:* 206–8.

7. Srivastava A, Khanduri A, Lakhtakia S, Pandey R. Falciparum malaria with acute liver failure. *Trop Gastroenterol* 1996; *17:* 172–4.

8. Permaratna R, Gunatilake AK, Desilva NR, Tilakaratney, Fonreka MM, Desilva HJ. Severe hepatic dysfunction associated with falciparum malaria. *Southeast Asian J Trop Med Pub Hlth* 2001; *32:* 70–2.

9. Kochar DK, Agarwal P, Kochar SK, Jain R, Rawat N, Pokharna RK, Kachhawa S, Srivastava T. Hepatocyte dysfunction and hepatic encephalopathy in *Plasmodium falciparum* malaria. *Qtl J Med* 2003; *96:* 505–12.

10. Chawla LS, Sidhu G, Sabharwal BD, Bhatia KL, Sood A. Jaundice in *P. falciparum*. *J Assoc Phy India* 1989; *37*(6): 390–2.

11. Kochar DK, Singh P, Agarwal P, Kochar SK, Pokharna R, Sareen PR. Malarial hepatitis. *J Assoc Phys India* 2003; *51:* 1069–72.

12. Kochar DK, Saxena V, Singh Narvachan, Kochar SK, Kumar SV, Das A. *Plasmodium vivax* malaria. *Emer Infect Dis* (Serial on int.) 2005 http://www.cdc.gov/ncidod/EID/vol.11 no.01/04-0519, htm.

13. Hills AG. Malarial jaundice. *Am J Med Sci* 1971; *212:* 45–3.

14. Amaral CN, de Albuquerque YD, das Neves Pinto AY, de Souza JM. Importance of clinical and laboratory profiles for the differential diagnosis of malaria and acute viral hepatitis. *J Pediatr (Rio J)* 2003; *79*(5): 429–34 .

15. Kachawaha S, Pokharana R, Rawat N, Garg P, Badjatiya H, Kochar DK. Ultrasonography in malarial hepatitis. *Indian J Gastroenterol* 2003; *22*(3): 110.

Corresponding author: Dr. D.K. Kochar, C-54, Sadul Ganj, Bikaner–334 003 (Rajasthan), India
E-mail:drdkkochar@yahoo.com; drdkkochar@indiatimes.com

Received: 27 March 2006 *Accepted in revised form:* 29 May 2006