Falciparum Malaria or Fulminant Hepatic Failure?

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Tasnim Ahsan, S.M. Rab, M.S. Shekhani (Department of Medicine, Jinnah Postgraduate Medical Centre, Karachi.)

Abstract

Six cases of severe jaundice and encephaiopathy due to falciparum hepatitis initially diagnosed as fulminant hepatic failure are reported. This rare presentation of falciparum malaria should be suspected in patients with persistent fever, jaundice, encephalopathy and hepatomegaly. The diagnosis should be further suspected when the liver function tests show a predominantly conjugated hyperbilirubinemla with only modest elevation of liver enzymes and alkaline phosphatase. Liver biopsy is valuable in establishing the diagnosis at all stages of the disease (JPMA 43:206, 1993).

Introduction

Mild jaundice is a familiar manifestation of all types of malaria and is attributed to haemoiysis of parasitized red cells[1]. Mild hepatitis may contribute to this trivial hyperbilirubinemia, which has been reported in fatciparum as well as other types of malaria[1-3]. The many faces of falciparum malaria pose a constant diagnostic problem. Deep jaundice and encephalopathy is one such rare presentation which masquerades as fulminant hepatic failure. We report six cases of severe jaundice due to falciparum malaria seen over a period of 14 months.

Patients and Methods

Six patients initially diagnosed as hepatic encephalopathy due to fulminant hepatitis were seen. Five of them presented to one of the three general medical units at Jinnah Postgraduate Medical Centre, Karachi, admitting patients twice a week and one was seen by one of the authors in another hospital. There were five males and one female, who was not pregnant. Their ages ranged between 23-63 years with a mean age of 38 years. They were in good health previously with no history of jaundice in the past. No known hepatotoxic drug had been administered. All patients presented with fever ranging from 6 to 15 days, jaundice from 3 to 10 days and altered consciousness from 1 to 9 days before presenting to us. They were examined clinically and their complete blood counts, liver function tests including prothrombin time and serum proteins, urea, creatinine and electrolytes were done. Blood was also cultured and examined for malaria4 parasite and HbsAg. All patients were given intravenous quinine and supportive treatment. Two patients had to be dialyzed for associated renal failure. Liver function tests were repeated weekly in those who survived. Liver biopsy was obtained in 3 patients. In one patient it was taken at the onset of the illness, in the other at 4 weeks, when the liver function tests were normal and in the third patient an immediate postmortem biopsy was obtained. All patients had pyrexia ranging between 37.5°C to 39.5°C. They developed moderate to severe jaundice between 1-9 days (mean 5 days) and went on to develop various grades of encephalopathy, 2 to 12 days (mean 6 days) after the onset of fever (Table I).

Table I. Clinical parameters.

Case No.	Age and sex	Fever		Jaundice	Encephalopathy					Hepatomegaly	Splenomegaly	Outcome	
		Severity (°C)	Duration (Days)	Duration (Days)	1	2	3	4	Duration (days)	(cm)	(cm)	Complete Recovery	Fatal
1	24F	38	11	10			+		9	2	0	+	
2	23M	39	12	6	+				2	4	4	+	
3	33M	38.5	6	5			+		3	3	2		+ 48 Hrs.*
4	55M	38.5	10	3				+	1	3	0		+ 8 Hrs*
5	35M	38	15	4		+			3	2	0	+	
6	63M	37.5	10	4	+				3	2	0	+	

*Number of hours after admission

All patients had a sizeable tender hepatomegaly and two patients had a palpable spleen. There were no focal neurological signs. All patients had plasmodium falciparum in their peripheral blood smears, had negative blood cultures and were negative for HBsAg. G6PD estimation was normal in five patients in whom it was done. Two patients had haemoglobinuria indicating some degree of intravascular haemolysis. The haemoglobin ranged between 5.1 to 9.6 gm/dl with a mean of 7.6 gm/dl. Serum biirubin was more than 20 mg/dl in 3 patients (Table II).

Table II. Laboratory investigations.

	Normal values	Case numbers					
		1	2*	3+	4*+	5*	6
Total bilirubin	0-1.0 mg%	22.5	11.6	47.1	11.9	7.8	20.8
Conjugated bilirubin	0-0.25mg%	14.3	7.5	24.2	6.0	5.6	13.5
AST	Upto 37 u/l	155.0	67.2	203.0	185	51.6	-
ALT	Upto 40 u/l	94.0	41.8	141.0	170.0	30.3	58.0
Alkaline phosphatase	39-117 u/l	129	93	154	110.0	115	60
Prothrombin time	Control 13 secs.	17	20	16	-	-	17
Serum NH3	17-18 ug/dl	182	90	-	-	-	-
Serum albumin	3.8-4.4 gm/dl	3.4	2.8	2.7	-	3.1	1.7
Urea	10-40 mg%	40.0	18.4	210	288.0	372.0	68.0
Creatinine	0.5-1.1 mg%	0.8	0.8	9.7	4.4	14.1	4.5

*Patients in whom liver biopsy was done
+ Patients who expired

The predominant abnormality was a conjugated hyperbilirubinemia. AST and ALT were mildly elevated and ranged between 51 to 203 u/i and 30 to 170 u/i respectively. Despite the conjugated hyperbilirubinemia alkaline phosphatase elevation was modest and only two patients had a raised alkaline phosphatase at the time of presentation. In all surviving patients alkaline phosphatase rose in the subsequent weeks as the biirubm level fell and normalized completely in four weeks. Prothrombin time was mildly disturbed in the four patients in whom it was done. Serum albumin was checked in five patients and was consistently low ranging between 1.7 to 3.4 gm/dl. Serum urea and creatinine were elevated in four patients and one more patient went on to develop renal failure later on. All three liver biopsies showed intact lobular architecture and swollen hepatocytes with dilatation of sinusoids, which were lined by plump hyperplastic kupifer cells. Brownish-black granular malarial pigment was seen within the sinusoids, cytoplasm of the kupifer cells and to a lesser degree in the cytoplasm of the hepatocytes. In the biopsy done in the acute stage, the portal triads additionally showed mild mononuclear cell infiltration and the sinusoids contained a large number of mononuclear cells some of which were haemopoietic. Some megakaryocytes were also seen, suggesting extramedullary haemopoiesis. Biopsy done after clinical and biochemical recovery showed slight dilatation of portal tracts with mild chronic inflammatory cell infiltration and some stellate fibrosis. The postmortem biopsy showed extensive acute fatty inifitration of hepatocyte with some areas of liver necrosis and few councilman bodies. Two patients died, one expired shortly after admission and the other was anuric and

hyperkalemic. He was shifted to the renal unit for dialysis where he expired. The remaining four patients recovered completely in four weeks.

Discussion

Fever, jaundice and alteration of consciousness is not an uncommon scenario in a tropical country like ours. All the six cases reported here were initially thought to have fulminant hepatic failure due to viral hepatitis. This diagnosis has been uniformly recorded initially in all similar cases reported in literature[4-8]. However, there were several features in the history, clinical presentation and laboratory data of these cases which made us review the initial diagnosis. Fever was persistent even after jaundice had appeared. The liver which is almost always shrunken in fulminant hepatic failure was markedly enlarged and tender in our cases. The main abnormality in LFTs was a marked elevation of serum bilirubin predominantly of the conjugated variety with a relatively mild elevation of liver enzymes, a fact which was strongly against fulminant hepatic failure[4]. The elevation of AST was more than ALT, presumably because of the contribution of haemolyzing red cells to this enzyme. There was only a modest derangement of prothrombin time and none of the patients had any abnormal bleeding unlike fulminant hepatic failure. Significant hypoalbuminemia was a regular feature despite the fact that patients were in good health previously. The hypercatabolism associated with falciparum malaria may be an explanation for this abnormality. Cerebral malaria was an unlikely contender in view of the slow evolution of alteration of consciousness progressing from a confusional to a stuporous state and finally to deeper levels of coma, very much like the progression of hepatic encephalopathy. The absence of any neurological deficit and epileptiform convulsions was also unlike cerebral malaria. Four out of six cases, had additional renal failure at the time of presentation and one more patient went on to develop renal failure when she was recovering from jaundice and encephalopathy. Renal failure is well documented in falciparum malaria. Only two of our cases had modest haemoglobinuria and none had any deficiency of G6PD. The direct effect of plasmodium falciparum in obstructing circulation in the renal capillaries might be the major contributor to renal failure[9]. It seems unlikely that renal complications of falciparum malaria have any contribution in the genesis of this rare presentation, because we were treating cases of acute renal failure induced by falciparum malaria and no hepatitis at the saxne time. Two of our cases had no evidence of renal failure at the time of presentation and yet they had grade III and grade I encephalopathy respectively. Renal failure contributes significantly to the mortality of falciparum hepatitis as both our fatal cases had profound uraema. Precisely what is it that causes the encephalopathy is a matter for speculation and further research, because unlike fulminant hepatitis[1], the hepatocyte itself is not very severely affected. This is evidenced by the mild derangement of liver enzymes, prothrombin time as well as liver histology. Why some patients suffering from falciparum malaria should develop profound jaundice and progress to encephalopathy remains unclear. Some as yet unidentified host factor maybe responsible for this, as may some environmental factor in view of the fact that all our cases were seen in winter months only. While severe jaundice is not a very common mode of presentation of falciparum malaria it is not that rare either. Six cases were identified by us over a 14 month period. Joshi et al[4] also reported 9 cases over a 2 year period. The histopathological examination - of three differently timed liver biopsies show changes that are very specific and diagnostic of malarial hepatitis at all stages of the disease. The immediate postmortem liver biopsy obtained in one fatal case showed changes of sufficient hepatic injury that could have been the primary cause of death. An early liver biopsy may be very valuable in establishing the diagnosis of malaria hepatitis in unusual cases of jaundice. In countries like Pakistan, where febrile illnesses with jaundice and alteration of consciousness are commonly encountered, it is vital to carefully differentiate between viral hepatitis, malarial hepatitis and typhoid hepatitis. Whereas the treatment for viral hepatitis is only supportive, for the other two conditions the treatment should be

prompt and specific. We submit that falciparum malaria should be considered as a strong possibility in patients with persistent fever, jaundice, encephalopathy and hepatomegaly, who also show a predominant conjugated hyperbiirubinemia, normal or mildly raised alkaline phosphatase, mild derangement of AST, ALT, prothrombin time and hypoalbuminemia. Associated renal failure should also be sought and treated as it may be an important contributor to the mortality.

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