

CASE REPORT

SEVERE HEPATIC DYSFUNCTION ASSOCIATED WITH FALCIPARUM MALARIA

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Abstract. We describe severe hepatic dysfunction associated with an attack of falciparum malaria in six Sri Lankan patients. Clinicians working in areas endemic for malaria should be made aware of this unusual complication.

Severe and complicated falciparum malaria can cause many clinical syndromes. These include cerebral malaria, severe hemolysis, cerebellar manifestations, acute renal failure, diarrhea, algid malaria and striated muscle necrosis. hyperbilirubinemia is common, but is predominantly unconjugated. Signs of hepatic dysfunction are unusual (WHO, 2000). However there have been few isolated reports of conjugated hyperbilirubinemia, low and falling serum albumin levels, significant increase in amino transferases and moderate prolongation of prothrombin time: all indicative of hepatic dysfunction. A malarial "hepatitis syndrome" has also been described, but almost exclusively from India (Srivastava *et al.*, 1996).

Over a period of eight months since June 1999, six patients [mean age 31 (range 13 - 45), four males] were admitted to our unit with high fever, headache and vomiting. Four of these patients were residents of Colombo district (non-endemic) who had visited Anuradhapura during a malaria epidemic in the North Central Province 2-6 weeks prior to admission. The other two were soldiers who were serving in

Jaffna in the Northern Province, which is also endemic for malaria. The fever was 3-6 days in duration and was associated with chills and rigors. All had severe vomiting and one had hematemesis. Except for the two soldiers, others had no exposure to muddy water, and none had severe body aches or muscle tenderness. Although three of them consumed alcohol occasionally, they had not consumed alcohol during the two months prior to this illness. None had a history of ingesting hepatotoxic drugs or contact with viral hepatitis. There was no past history of jaundice. On examination at admission, they were deeply icteric and pale with mild hepato-splenomegaly. None of them had stigmata of chronic liver disease. On the second day of admission two patients developed drowsiness with constructional apraxia, and one had flapping tremors. One patient developed moderate ascites and another developed a generalized convulsion on the day of admission but had no neck stiffness or papilledema. Thin blood films of all patients showed a high *Plasmodium falciparum* parasitemia. Results of other investigations before treatment and on discharge from hospital are shown in Table 1. In addition to the investigations shown in the table serology was negative for *Leptospira*, Hepatitis A, B, C, E, dengue and hanta viruses. There was no evidence of intra hepatic or extra hepatic bile duct dilatation on ultrasound

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scanning, and the urinary D-dimer level was less than 250 ng/ml.

All six patients were treated with intravenous quinine for seven days as chloroquine resistance is now widespread in Sri Lanka. They were transfused with packed red cells, platelets, fresh frozen plasma and treated with vitamin K and lactulose as indicated. The clinical condition and many of the biochemical parameters improved within 5 days of quinine therapy. At follow up 3-4 weeks after discharge from hospital, the patients were well and serum bilirubin levels had returned to normal.

In all our patients, falciparum malaria was associated with features suggestive of severe hepatic dysfunction. They were deeply icteric and liver function tests suggested hepatic decompensation. These features initially suggested to us a diagnosis of viral hepatitis which is common in this country, but the presence of high fever with rigors and the

strong history of a visit or stay in an endemic area made us investigate the patients for malaria. Blood films confirmed severe falciparum malaria. The excellent response to quinine therapy made it very likely that the hepatic dysfunction was causally related to the malarial infection.

Although documented in India and Pakistan during 1992-1996 (Anand *et al*, 1992; Mishra *et al*, 1992; Ahsan *et al*, 1993), "malarial hepatitis" has not been described as a complication of falciparum malaria in other countries, including Sri Lanka. The features of patients with "malarial hepatitis" described in India show many similarities to our patients (Srivastava *et al*, 1996). Several of the Indian patients had direct hyperbilirubinemia with high alkaline phosphatase and mild to moderate increases in serum transaminases. They also showed a reduction in serum protein levels and prolongation of prothrombin time. Liver biopsy in a few patients showed Kupffer cell hyper-

Table 1
Investigations in the six patients with falciparum malaria.

Time :	Before treatment with quinine		On discharge	
	Median	Range	Median	Range
Hemoglobin (g/dl)	6.8	5.5 - 8.2	10.5	9.5 - 12.6
Reticulocyte count	2.6%	1.1 - 3.2	2.2%	1.8 - 3.5%
White cells: total (x 10 ⁹ /l)	3.8	2.5 - 5.3	6.2	5.8 - 7.6
Neutrophils	34%	28 - 45%	54%	34 - 65%
Lymphocytes	58%	40 - 63%	36%	31 - 58%
Platelet count (x 10 ⁹ /l)	64	45 - 78	260	105 - 430
Urine bilirubin	++	+ - ++	-	- to +
Urobilinogen	+	+	+	- to +
Serum bilirubin (mg/dl)	24.5	17 - 38	1.9	1.1 - 2.8
Direct bilirubin (mg/dl)	19.2	12.3 - 26.7	0.9	0.6 - 1.8
Indirect: bilirubin (mg/dl)	5.3	4.7 - 11.2	1.0	0.5 - 1.0
Serum AST(IU/l) (n=0-35)	176	93 - 370	36	32 - 43
Serum ALT(IU/l) (n=0-35)	138	84 - 390	30	30 - 45
Alkaline phosphatase (IU/l) (n=98-279)	262	165 - 303	102	96 - 123
Gamma GT (IU/l) (n=11-50)	72	66 - 96	20	18 - 30
Prothrombin time (control=12 seconds)	18	14 - 28	12	12 - 13
Serum proteins (g/l)	5.6	5.2 - 6.4	6.1	5.8 - 7.9
Albumin (g/l)	2.8	2.3 - 3.0	4.2	3.5 - 4.8
Globulin (g/l)	3.2	2.9 - 3.4	1.9	2.3 - 3.1
<i>P. falciparum</i> (parasites/ml)	45x10 ³	28 - 55	Nil	Nil

plasia and deposition of malarial pigment in the liver, and one patient had parasitized red cells in the hepatic sinusoids (Anand *et al*, 1992). Although the term "hepatitis" may not be appropriate as the aminotransferases were not elevated to levels seen in viral hepatitis, the evidence of liver cell dysfunction in the Indian patients and in our patients is strong.

The pathogenesis of this complication is poorly understood. Possible mechanisms may include congestion of the hepatic sinusoids caused by parasitized red cells or the effect of cytokines such as TNF α , which are released in high concentrations in severe falciparum malaria, causing hepatic dysfunction. Our patients also had low total white cell counts with relative neutropenia and thrombocytopenia. These changes which are well known to occur in severe malaria could also be due to cytokine induced bone marrow suppression, sequestration of white cells and platelets in the spleen, or due to disseminated intravascular coagulation (DIC) (Bradley *et al*, 1996). Normal urinary D dimer levels make DIC unlikely in our patients.

Treatment with standard doses of quinine in patients with "malarial hepatitis" can result in quinine toxicity (Karbawang *et al*, 1993), but none of our patients developed this compli-

cation. In fact, the response to quinine therapy was dramatic in all our patients.

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