COMPLICATED FALCIPARUM MALARIA

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ABSTRACT

We studied 50 cases of complicated falciparum malaria in order to evaluate the different clinical presentations. Thirty five had cerebral malaria while 15 presented with extracerebral features including diarrhea and vomiting (n=6), hepatitis (n=4), acute renal failure (n=3), and gastrointestinal bleeding (n=2). These cases were treated with quinine. Mortality was higher in extracerebral form (33.3%) as compared to cerebral malaria (22%). Our study suggests that even though cerebral malaria remains the single most important cause of high mortality in complicated falciparum malaria, extracerebral presentation of falciparum malaria is equally life threatening and should be viewed seriously.

Key words: *Falciparum malaria, Cerebral malaria.*

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Falciparum malaria continues to be one of the leading causes of morbidity and mortality (1). It has varied modes of presentation with occasional life threatening complications(2). The definition of complicated *Plasmodium falciparum* malaria is conflicting. The most appropriate acceptable definition of severe and complicated falciparum malaria is recognition of any one or more of the clinical features such as cerebral malaria, jaundice, renal failure, pulmonary edema, hypoglycemia, circulatory collapse, spontaneous bleeding, repeated generalized convulsions and acidosis(l). In order to evaluate the clinical features and outcome of complicated *Plasmodium falciparum* malaria, we prospectively studied 50 such patients.

Material and Methods

During January 1989 to December 1991 we carried out a prospective study of confirmed *Plasmodium falciparum* malaria. Out of 200 patients, 50 patients (25%) who met the criteria of complicated P. *falciparum* malaria were included in this study. A thorough clinical examination was carried out and thick and thin blood smears stained with Leishman's stain were examined for P. *falciparum.* Cerebral malaria was diagnosed in patients with persistent altered sensorium in addition to smear positive for schizont of P. *falciparum.* Complete hematological profile was obtained in each case. Biochemical investigations included serum bilirubin (both conjugated and unconjugated), SGOT, SGPT, 24 h urinary output, urine routine and microscopic examination, blood urea and serum creatinine. Platelet count; and bleeding, clotting and prothrombin times were carried out in patients with bleeding disorder. Patients with jaundice or renal failure were investigated for intravascular hemolysis. Peripheral smear for broken and

fragmented red cell and urine benzidine test for hemoglobinuria were looked for. Cerebrospinal fluid (CSF) examination was done in those patients with neck stiffness, positive Kernig's sign and focal neurological deficits. Patients known to have renal involvement, diabetes mellitus and hepatitis earlier were excluded.

All patients were treated with intravenous quinine 10 mg/kg infused every 12 h for 3-4 day? followed by a single dose of sulphadoxin-pyrimethamin. Other supportive measures to combat diarrhea, vomiting or convulsions were carried out simultaneously.

Results

There were 36 males and 14 females in the age group of 8 months to 12 years. Twenty seven cases were below 5 years, 20 between 6 and 10 years and 3 above 10 years. Thirty five patients presented with cerebral malaria while 15 manifested extracerebral features. Since most of the clinicians were quite familiar with cerebral malaria, the index of suspicion was high. However, the same cannot be said for extracerebral involvement. Hence, it is possible that some of the less sick extracerebral *P. falciparum* malaria might have been missed during the study. The various clinical and abnormal laboratory parameters are represented in *Tables I & II.*

Forty eight patients were febrile and 2 patients who presented with cold and clammy condition were afebrile throughout their illness but had diarrhea and vomiting, imperceptible pulse and were diagnosed to have peripheral circulatory failure. These two patients had smear positive for *P. falciparum.*

TABLE I–*Clinical Profile and Outcome of P. falciparum Malaria*

	Type	0-5 yr (n=27)	6-10 yr (n=20)	11-12 yr (n=3)	Mortality
A.	Cerebral (n=35)	20 (6)	12 (1)	3 (1)	8 (22%)
	* Altered sensorium	20 (2)	12 (1)	3 (1)	
	* Convulsion	14 (3)	8	2	
	* Raised ICT	7	3	-	
	* Meningeal signs	6 (1)	2	-	
	* Hemiparesis	1	1	-	
B.	Extracerebral (n=15)	7 (3)	8 (2)	-	5 (33.3%)
	* Diarrhea, vomiting and circulatory collapse	4 (2)	2	-	
	* GI bleeding	-	2 (1)	-	
	* Hepatitis	2	2	-	
	* Acute renal failure	1 (1)	2 (1)	-	

Numbers in parentheses indicate mortality.

TABLE II—*Abnormal Laboratory Parameters*

A.	Cerebral malaria (n=35)	CSF (Mean values)		
	Meningeal signs (n=8)	(*i*) Protein (mg/dl) 60 ± 5(n=5) 30 ± 5(n=3)	(*ii*) Sugar (mg/dl) 55 ± 5	(*iii*) Cells 8 ± 2 (lymphocytes)
B.	Extra cerebral malaria (n=15)			
	Diarrhea, vomiting and circulatory collapse	Serum Na ± (mEq/L) 120 ± 2.5	Serum K ± (mEq/L) 2 ± 0.5	
	Hepatitis	Serum bilirubin (mg/dl) 6	SGOT (IU/L) 80 ± 2	SGPT (IU/L) 102 ± 5.2
	ARF	Blood urea (mg/dl) 88 ± 3		*S. creatinine* (mg/dl) 6.2 ± 1

All 35 patients with cerebral malaria presented with altered sensorium; 24 had convulsions and 10 had persistent headache and vomiting which got relieved after intravenous mannitol infusion. These are the cases which were documented to have raised intracranial tension. Meningeal signs and hemiparesis were observed in 8 and 2 patients, respectively. CSF was studied in 8 patients with meningeal signs. Cytological and biochemical study was normal in all cases except in 5 patients where the protein was moderately raised. In all these patients, blood glucose was in the range of 80-110 mg/dl. Eight patients (22%) succumbed on 2nd and 3rd day of quinine therapy. The duration of unconsciousness was 24 h in 1, 36 h in 2 and 48 hours in 5 patients. Persistent convulsions and delay in hospitalization beyond 24 hours were seen in 4 and 6 patients, respectively.

Out of the 15 extracerebral presentations diarrhea and vomiting, hematemesis, jaundice and oliguria were observed in 6, 2, 4 and 3 patients, respectively. No discernible cause was identified on history, endoscopic examination and coagulation profile study in patients with gastrointestinal bleeding. All the 6 cases with diarrhea and vomiting had dehydration and circulatory collapse. Two out of six died due to irreversible circulatory failure. Hepatosplenomegaly was the consistent finding in all 4 cases of jaundice. Out of 4 cases, one each had conjugated hyperbilirubinemia and two had mixed type. Hepatitis B surface antigen were negative in all cases. Serum bilirubin came down to normal within 4 to 6 days of hospital stay in all these patients.

Two out of three patients of renal failure died in 2nd and 4th hours after admission. One patient survived following dialysis. Intravascular hemolysis was never a feature of all these patients with jaundice and renal failure, as none of them had fragmented and broken red cell nor hemoglobinuria in the urine.

Discussion

Much of the concern about falciparum

malaria has centered around cerebral malaria(3). There are few reports on extracerebral complications of *P. falciparum* malaria. Cerebral involvement, a well known entity of falciparum malaria was encountered in 70% of patients in this study which is similar to that reported previously(2,4). Although cerebral involvement is believed to occur as a consequence of sequestration of parasitized red blood cells in the capillaries(5), the same type of vascular changes have been observed in patients who died without developing cerebral malaria(6). There is still no adequate pathological explanation for this even though local' anoxia, metabolic derangement and action of endogenous mediators have all been proposed as possible factors. In the present study, mortality was observed in 8 patients (22%). Factors contributing to mortality were duration of unconsciousness, persistent convulsions and delay in institution of therapy. Delay in institution of therapy was the remarkable finding in this study when compared with the mortality rate of other Western authors(3) and was attributed to blind belief and illiteracy.

Of the 50 cases, 4 patients (8%) had jaundice, and this is almost similar to the series of Ramchandran *et al.(7)* and Gupta *et al.* (8). Rise of serum bilirub'in in falciparum malaria patients is considered to be due to hemolysis of peripheral parasitized red blood cell, and impairment in bilirubin transport because of reticulo endothelial blockage and disturbances of hepatocyte microvilli(2). Thus the conjugated, unconjugated and mixed type of hyperbilirubinemia observed in the present study might be due to aforementioned reasons. Fatty changes, liver cell necrosis, nuclear vacuolation and liver cell congestion have been observed in falciparum malaria infection(9). Hence, it is reasonable to say that the rise in level of transaminase in the present series could be due to liver cell damage. It is unlikely to be due to viral hepatitis because in all of these cases, jaundice disappeared quickly after the treatment of malaria.

Of the 6 patients with diarrhea, vomiting and circulatory collapse, 4 were febrile and two were afebrile throughout their illness. The latter group had irreversible circulatory collapse and shock. Nausea, vomiting and diarrhea are common in malaria. Biopsies of the gut indicates parasite sequestration in the vascular bed which presumably interferes with the absorptive processes(l) causing vomiting and diarrhea. It is possible that a similar mechanism might be the operative factor in the present series. This is of great practical importance in children with *P. falciparum* malaria as the condition is often associated with electrolyte imbalance and circulatory collapse causing considerable morbidity and mortality.

Two patients presented with upper gastrointestinal bleeding. Similar presentations have been described previously(2,10). While the exact pathophysiology is not well defined, the gut involvement in falciparum malaria is considered to be due to vascular congestion and sloughing of mucosa, leading to diarrhea, vomiting and gastrointestinal bleeding(ll). The lone patient in this group died due to shock. The other patient revealed no gastrointestinal pathology on gastroscopy and barium meal X-ray of stomach and duodenum. No obvious history of gastric irritant and analgesic intake was available; hence it was attributed to *P. falciparum* malaria.

Of the 3 patients with renal failure, 2 patients had additional features of peripheral circulatory failure and shock. It is unlikely to be hemolytic uremic syndrome as none of them had evidence of intravascular hemolysis. Hence, it is possible that cortical

ischemia or tubular necrosis as a result of persistent low renal perfusion could be responsible for the acute renal failure. However, the possibility of algid malaria as a primary pathology can not be ruled out.

Even though cerebral malaria remains the single most important cause of high mortality in complicated malaria, extracerebral presentation is also equally life threatening. It is to be stressed that most of the clinicians and health workers are quite familiar with the clinical profile of cerebral malaria but the same is not true for extracerebral involvement, where the index of suspicion is low. Hence, some of the cases with extracerebral involvement might have escaped the attention of clinicians and/or health workers. Those at risk with any of the atypical presentation should be screened out for *P. falciparum* malaria. Recognition of any or more of the aforesaid clinical features should raise the suspicion of severe and complicated falciparum malaria.

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