SEVERE AND COMPLICATED MALARIA IN BIKANER (RAJASTHAN), WESTERN INDIA

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Abstract. Severe and complicated malaria is an important cause of mortality in *Plasmodium falciparum* infection. We describe in this study the details of 532 cases of such syndromes admitted to hospital during an outbreak of malaria between September-December 1994. Increase in the annual rain fall, collection of water around Indra Gandhi Canal, forestation of shrubs around it and migration of labor, adaptation of *Anopheles stephensi* to desert climate and favorable breeding of *An. culicifacies* in the areas under impact of irrigation were presumptive causes of the outbreak in this region. Cerebral malaria (25.75%), hepatic involvement (11.47%), spontaneous bleeding (9.58%), hemoglobinuria (7.89%), severe anemia (5.83%), algid malaria (5.26%), ARDS (3%) and renal failure (2.07%) were the important manifestations. The overall mortality was 11.09%, which was high because of infection in the non-immune population of this area. Ignorance about the severity of this disease and lack of transportation facility was another important factor. Morality was highest in ARDS (81.25%) followed by severe anemia (70.97%), algid malaria (46.43%), renal failure (45.45%), jaundice (36.06%) and cerebral malaria (33.57%). Pregnancy was an important determinant increasing the mortality in female patients. Mortality was very high (82.35%) in those persons who presented with more than 3 syndromes together.

INTRODUCTION

Plasmodium falciparum infection causes the most serious form of malaria and is a common cause of mortility in the tropics (WHO, 1991). Infections with this parasite can be fatal in the absence of prompt recognition of the disease and its complications, however, active and appropriate patient management can save a number of lives (WHO, 1991; Warrell *et al*, 1990).

Severe and complicated falciparum malaria is defined (Warrell *et al*, 1990; Stephen, 1992) by the presence of one or more pernicious signs and symptoms in a patient showing asexual parasitemia of *Plasmodium falciparum* in the peripheral blood. It is important to appreciate that these severe manifestations can occur singly, or more commonly in combination in the same patient.

Bikaner district (Fig 1) is a part of western Rajasthan (India) situated along the Indo-Pakistan border. It is a desert zone having dry weather with an annual rainfall of 26.3 cm and the temperature ranging from 0°C to 49°C. There has been a change in the ecosystem in the recent years causing an increase in the annual rainfall. There has also been a good collection of water at different sites in water bodies around the Indira Gandhi Canal. *Plasmodium falciparum* malaria had been prevalent in this region in the last few years. The area was hit severely by it in 1992 after heavy rainfall following a long dry spell. Scattered cases were being recorded in whole of 1993 and upto August, 1994. There was a severe outbreak of malaria in September, 1994, again after heavy rainfall during July-August 1994.

The important cause of mortality in *Plasmodium falciparum* infection is due to severe and complicated malaria. The details of morbidity and mortality of different syndromes associated with severe and complicated falciparum malaria is not available in the Indian literature in detail and thus we decided to identify and categorise the patients admitted during the outbreak of 1994 into different syndromes and studying the trend of mortality caused by them.

We report a study of 532 cases of severe and complicated falciparum malaria admitted and treated at this tertiary level of health care system (WHO, 1990) at SP Medical College and associated group of hospitals, Bikaner (Raj) India.

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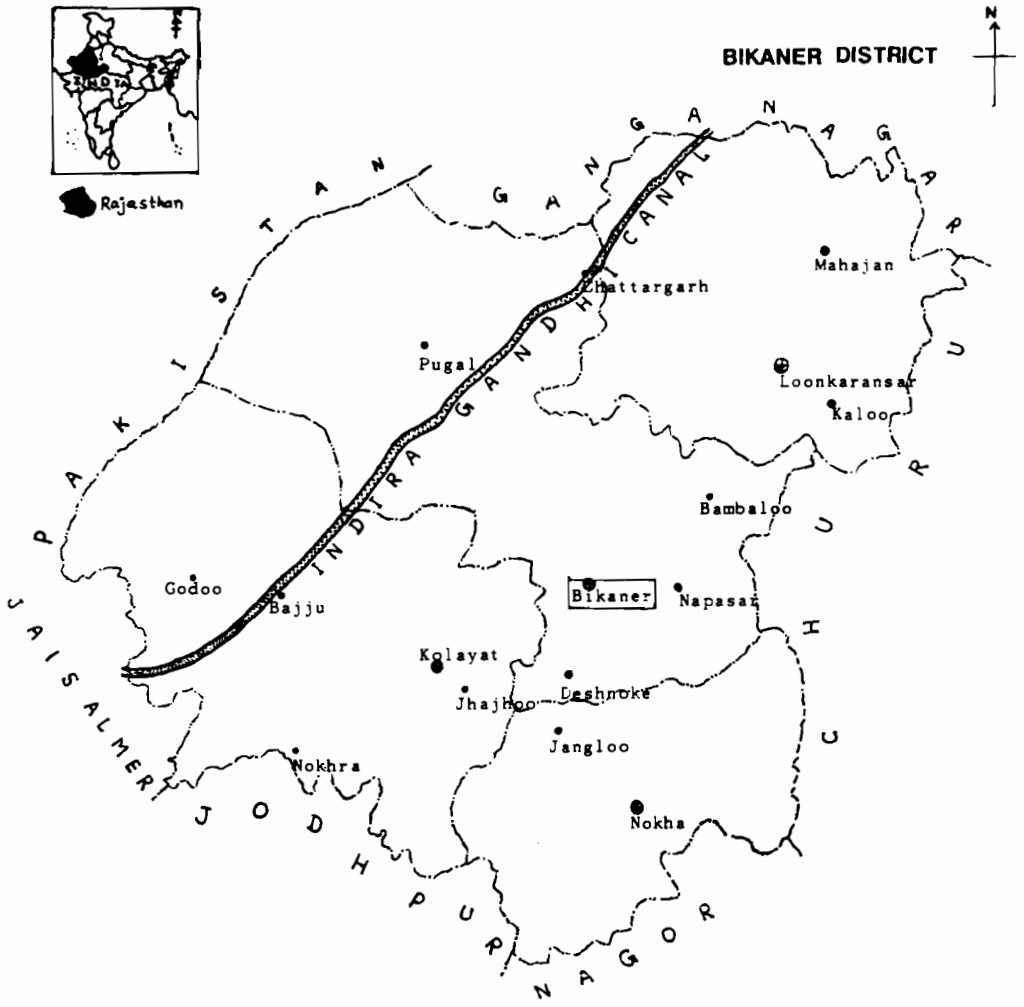

Fig 1–Bikaner District.

MATERIALS AND METHODS

Bikaner district is a part of the Thar desert, having a population density of 44/km². The health system in the district is constituted by 31 primary health centers and 166 subcenters, providing all essential preventive and curative health care. It is primarily a non-endemic area for malaria but in September 1994, after a heavy rainfall in the month of July, we became alarmed at the number of patients from all over the district. Additional health measures were taken and the whole area was covered by 28 mobile medical teams (each having a doctor and a technician) providing prophylactic and curative treatment of malaria upto the most peripheral part of the district.

The health care system was divided into 3 categories according to WHO (1990) and all patients of severe and complicated malaria (category III) were treated at a tertiary level hospital, situated at Bikaner. This was the only tertiary level center where specialized health care was delivered for the population covering an area of 27,244 km². A semi-intensive care unit was created to manage the malaria patients in 2 separate wards (having a capacity of 45 beds each). The patient: nursing staff ratio was 4.5:1. Each ward was divided into 4 segments and the treatment was supervised by a

team. Round the clock resident doctors were available in both wards. One laboratory technician was present all the time to examine the blood slides.

The total admissions during September-December, 1994, were 1600. Thick and thin blood smears were collected from all the patients immediately after admission before any treatment. Those patients who had evidence of vivax malaria or in whom the blood slide was negative were not included in the study. After initial clinical and laboratory examination (hemoglobin, packed cell volume, total and differential leukocyte count, blood glucose level (at time of admission), serum creatinine, serum bilirubin, cerebrospinal fluid (CSF) and fundus examination in unconscious patients, the patients were categerised as simple malaria (group I) and severe and complicated malaria (group II) according to WHO (Warrell *et al*, 1990) definition. This study was conducted only in the 532 patients of group II. Prothrombin time, bleeding time, clotting time, and platelet count were done only in those patients who had evidence of bleeding tendency. Upper gastrointestinal endoscopy was done in all the patients having hemetemesis. Test for HbsAg was done in all patients who had evidence of jaundice and only HbsAg negative patients were included in the study.

The detailed parameters of each patient were recorded in a proforma designed by WHO (Warrell *et al*, 1990) and additional specific signs and symptoms were also noted. Specific treatment was instituted in all the patients in the form of intravenous quinine dihydrochloride 7mg/kg loading dose in half an hour followed by 10mg/kg/8 hourly for 7 days (Stephen, 1992; WHO, 1990). As soon as the patient was able to take oral medication the IV drugs were stopped and the patient was put on oral therapy according to WHO (1990). A loading dose was not given to patients who received the drug at the primary/secondary health care station. A close observation was made of each patient and the data were recorded every day in the proforma. The specific syndromes were defined and the treatment was instituted accordingly (WHO, 1991).

The patients with acute renal failure were put on hemodialysis. The patients with severe shock were screened for evidence of infection by repeated blood counts, blood culture and urine culture. All patiens with septicemia received ceftriaxone along with amikacin/gentamicin and switched to specific antibiotics after receipt of the report of culture and sensitivity. All patients with pulmonary edema received intravenous aminophyllin, oxygen, frusemide and judicious control of fluids. Hypoglycemia was treated by 25% glucose infusion. Convulsions were treated by intravenous dilantin and diazepam followed by oral dilantin for a period of 1-2 months. Psychosis was treated with oral haloperidol and alprazolam along with parentral diazepam as and when required. Further treatment was carried out after consultation with a psychiatrist.

Thin and thick smears were examined in all the patients. The categorization of different syndromes was further confirmed at the time of discharge/after death. As the pregnancy is also an important factor which influences the course of illness, its effect was studied separately and was compared with simillar illness in non-pregnant women.

RESULTS

A total of 1,600 patients were admitted in 4 months out of which 532 were categorized in different malaria syndromes. This number included 314 males and 218 females (aged between 14-74 years) amongs them 30 females were pregnant at different periods of gestation.

The distribution and number of deaths seen in individual syndromes are given in Table 1. Fifty-one patients had overlapping syndromes. The overall mortality was 11.09% (59 deaths), higher in females (16.06%) than males (7.64%). The details of the morbidity and mortality in pregnant women are depicted in Fig 2.

Hemoglobin estimation revealed anemia (Hb < 11g%) in 86% patients and severe anemia (Hb < 5g%, packed cell volume < 15%) was present in 31 (5.83%) patients. Total leukocyte count (TLC) was within normal limits (4,000-12,000/mm^3) in 88% (468) patients. Leukopenia (< 4,000/mm^3) was present in 3.95% (21) and leukocytosis (> 12,000/mm^3) was present in 8.08% (43) patients. Elevated serum bilirubin (> 3mg/dl) was detected in 61 (11.47%) patients. High serum creatinine level (> 3 mg/dl) was present in 11 (2.07%) patients. Blood glucose estimation done at the time of admission revealed blood glucose level < 40 mg/dl in 11 (2.07%) patients and between 41-60 mg/dl in 18 (3.83%) patients.

CSF examination in patients with cerebral malaria revealed increased pressure in 20% (28). CSF

Table 1

Incidence and mortality in various pernicious syndromes in 532 cases of severe and complicated malaria.

Syndrome	No. (%) of cases	No (%) of death
A) Cerebral malaria	137 (25.75%)	46 (33.57%)
Male	70 (51.09%)	19 (27.14%)
Female	67 (48.91%)	27 (40.29%)
B) Severe anemia (Hb < 5 g%)	31 (5.83%)	22 (70.97%)
C) Renal failure	11 (2.07%)	5 (45.45%)
D) Pulmonary edema (ARDS)	16 (3.00%)	13 (81.25%)
E) Hypoglycemia	11 (2.07%)	3 (27.27%)
F) Circulatory collapse, shock	28 (5.26%)	13 (46.43%)
G) Spontaneous bleeding	51 (9.58%)	4 (7.84%)
Hemetemesis and/or malena	18	
Bleeding gums	6	
Epistaxis	4	
Subconjunctival hemorrhage	4	
Hematuria	2	
Retinal hemorrhages	16	
Foot gangrene	1	
H) Repeated generalized-convulsion (other than cases of cerebral malaria)	13 (2.44%)	1 (7.69%)
I) Macroscopic hemoglobinuria	42 (7.89%)	4 (9.52%)
J) Impaired consciousness (but arousable)	34 (6.39%)	1 (2.94%)
K) Prostration, weakness	68 (12.78%)	2 (2.94%)
L) Jaundice (S. bilirubin > 3 mg/dl)	61 (11.47%)	22 (36.06%)
M Hyperpyerexia	132 (24.81%)	20 (15.15%)
N) Psychosis	11 (2.07%)	2 (18.18%)
O) Multiple factors (> 3)	51 (9.59%)	42 (82.35%)

protein, sugar and cells were within normal limits in all these patients. Fundus examination done in patients of cerebral malaria (137) revealed papilledema in 9 (6.57%), retinal hemorrhage in 7 (5.91%) and retinal hemorrhage with papilledema in 5 (3.65%) patients.

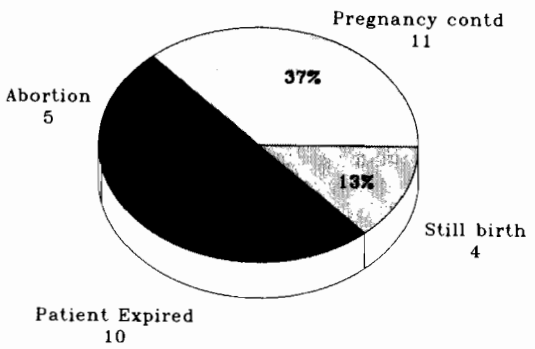

Fig 2–Outcome of severe malaria in pregnant women (n = 30).

Upper gastrointenstinal endoscopy was done in 15 patients who were having hemetemesis. In 5 patients erosion and congestion was detected in the first part of the duodenum, in 4 patients erosion was found in antral part of stomach and in 3 patients there was slight congestion and erosion at the lower end of the esophagus. However, in 3 patients no abnormality could be detected.

DISCUSSION

Severe and complicated malaria is the most important cause of mortality in *Plasmodium falciparum* infection (WHO, 1991). Depending on the severity and rapidity of parasitic infection and

the immune response of the host, the patient may have different types of clinical presentation (Ray *et al*, 1989). The patients in specific categories, *eg* extreme of age and pregnant women also have increased mortality (Warrell *et al*, 1990; Stephen, 1992).

Bikaner district is an arid zone which had recently experienced heavy rainfalls in the last few years. This region has always been regarded as a hypoendemic area for malaria (Sharma, 1986). The scenario of both disease morbidity and mortality seems to have altered to a great deal during the past decade, attributable to ecological and physiographical changes mainly due to the construction of the Indira Gandhi Canal and increased rainfall triggered by the El Nino Southern oscillation (ESNO) (Bauma and Van Der Kaay, 1994). The arrival of the canal in this desert region has resulted in a rise of the water table, water holding potential and plentiful growth of vegetation, particularly weeds. Along with this, the migration of labor from some malaria hyperendemic neighboring states to the site of the canal (Sharma and Kondrashin, 1991), adaptation of *An. stephensi* to the desert climate and favorable copious breeding of *An. culicifacies* in the areas under impact of irrigation (Tyagi, 1991), and increased trend of tolerance to DDT (the most commonly used insecticide in the malaria control program) by these vectors (Tyagi, 1995) created more favorable conditions for increased transmission of malaria. The present outbreak occurred in September-December. This is because of collection of water all over the region after heavy rainfall in July and August, causing an increase in the vector population. A similar observation was also noticed in a Balcad, Somalian study which reported a twenty fold increase in the incidence of *Plasmodium falciparum* malaria between 1986 and 1988 (Warsame *et al*, 1995).

Because of the severity of illness it is very essential to identify and treat the patients of *Plasmodium falciparum* malaria to diminish the chances of severe and complicated malaria. The treatment was thus provided at the furthmost points of the community by covering the population through mobile teams. As per WHO (1990) recommendations, preliminary treatment was provided at primary and secondary stations and only those who required IV medication or were having other pernicious syndromes were shifted to this tertiary station.

Plasmodium falciparum resistance for chloroquine is not studied in this area and thus as per WHO (1990) guidelines all patients were treated with IV quinine HCl. All the drugs needed for the management of patients were provided by hospital administration. Such recommendations have been also made by WHO (1993) putting the responsibility of proper availability and affordability of the drugs on the administration.

Out of total of 532 cases of severe and complicated malaria (age 14 to 74 years) the male and female ratio was 1.44:1. Overall mortality was 11.09% (59 deaths). The high mortality was probably because of the geographic situation of the area in which transportation facility from the remote area to the base hospital was severely lacking. This was also partly because of ignorance about the disease causing marked apathy towards getting the specific treatment. The mortality was greater in females (16.06%) in comparison to males (7.64%) because of specific neglect in getting rapid treatment for them and the deleterious effect of pregnancy.

The largest group of cases was of cerebral malaria (25.75%). Coma was present in all the cases and its depth and severity was assessed in each patient using the Glasgow coma scale; the majority of patients fell into score 3 to 6. This finding is consistent with Warrell *et al* (1990). The largest study in patients of cerebral malaria in Indian literature is by Dhamija *et al* (1991) describing 160 cases of this disease. They reported a fatal outcome in 19% patients, whereas in our series the mortality from cerebral malaria was 33.75%. This may be due to the fact that this area had witnessed *Plasmodium falciparum* malaria only in recent years (after 1992) and the population is largely non-immune, whereas the study of Dhamija *et al* (1991) in the North-East region was a longitudinal study spread over 15 years. Other reports of cerebral malaria involving a smaller number of patients are also available describing different trends of mortality (Panicker, 1986; Gopinathan *et al*, 1986; Upadhyaya and Bhalla, 1987; Mehta *et al*, 1989). Convulsions without coma were present in 3.29% cases and they were not included in the category of cerebral malaria. Proper diagnosis of hypoglycemia and prompt institution of treatment saved a majority of the patients with severe hypoglycemia.

Pulmonary edema (ARDS) is a grave and usually fatal manifestation of severe and complicated

malaria. The important feature of this complication is its appearance at the time when the patient starts showing signs of recovery usually after one or two days of treatment (Warrell *et al*, 1990). Pregnancy, renal failure and hypoglycemia are common predisposing factors. Tachypnea is the first manifestation of pulmonary edema. In our series 16 patients developed pulmonary edema, of which 4 were pregnant women who developed pulmonary edema just after delivery of the fetus. It is very grave complication and mortality contributed by it is high (81.25%). Various authors (Hall *et al*, 1975; White, 1986) have reported pulmonary edema in severe falciparum malaria but the exact cause of it is unknown. Possible pathogenic mechanisms are overhydration (Hall *et al*, 1975) and increased pulmonary capillary permeability (White, 1986) which might be due to the effects of endotoxins and cytokines.

Acute renal failure (ARF) is a sensitive prognostic indicator in severe falciparum malaria and is associated with high mortality. Various authors (Mishra *et al*, 1982; Mahakur *et al*, 1983; Dash *et al*, 1994; Boonpuncknavig and Sitprija, 1979; Philips *et al*, 1984) have described acute renal failure in severe falciparum malaria from India and elsewhere. In our series 11 patients had acute renal failure and mortality was 45.45% which is quite similar to the observations of Warrel *et al* (1990). The ARF was oliguric in 82% cases. Although the mechanism of acute tubular necrosis in malaria in adults is not clearly understood, increased blood viscosity and hypovolemia may be contributory factors (Warrell *et al*, 1990).

Macroscopic hemoglobinuria was present in 42 cases (7.89%) before starting quinine and the majority of patients (34) had cerebral malaria. We did not withhold quinine in these patients.

Circulatory collapse/algid malaria is also a complication of severe falciparum malaria. In our series 28 patients (5.26%) had circulatory collapse and the mortality attributed to it was 46.43%. Three patients had gram negative septicemia, 6 developed pulmonary edema, 4 had severe hemetemesis and 3 patients were severely dehydrated due to repeated vomiting and diarrhea. One patient had prolonged QTc and ventricular tachycardia while she was on IV quinine. The ventricular tachycardia was treated by stopping the quinine and starting intravenous magnesium sulfate (25%). The possible cause of algid malaria is gram negative septicemia, endotoxinemia due to passive absorption of endotoxin from the gut lumen resulting from cytoadherence of parasitized erythrocytes in small blood vessels in the villi leading to ischemic damage to endothelium (Warrell *et al*, 1990; Aung-Kyaw-Zaw *et al*, 1988).

Anemia is an inevitable consequence of severe falciparum malaria (Manson and Bell, 1987; Phillips *et al*, 1986). In our series 86% patients had hemoglobin levels below 11 g%. Severe anemia (Hb < 5 gm%) was present in 5.83% cases and it was associated with high mortality (70.97%). The mechanism of anemia is multifactorial and complex, involving hemolysis and inappropriate bone marrow response (Warrell *et al*, 1990). Spleen is the major site of destruction of red blood cells in malaria. Severe anemia is often associated with secondary bacterial infection, retinal hemorrhages and pregnancy.

Jaundice and hepatic dysfunction is also reported as an important pernicious syndrome in falciparum malaria by various authors (Gupta and Sikka, 1984; Agarwal *et al*, 1994; Warrell and Francis, 1990). In our series 61 (11.47%) patients had bilirubin concentrations more than 3 mg%. Hepatomegaly was present in 16.16% and splenomegaly in 63.15%. In most of these patients there was rise in indirect bilirubin concentration. Prothrombin time was prolonged in 22 patients. The mortality contributed by jaundice in severe falciparum malaria was 36.06%. Hyperbilirubinemia is attributable to intravascular hemolysis of parasitized erythrocytes, hepatic dysfunction and possibly an element of microangiopathic hemolysis associated with DIC (Warrell *et al*, 1990).

Hypoglycemia, associated with severe malaria had been reported by various authors from India (Das *et al*, 1988; Gopinathan, 1987) and other parts of world (White and Warrel, 1983; Fisher, 1983), is usually not suspected clinically. In a conscious patient it may present with classical symptoms of anxiety, breathlessness, oliguria, a feeling of coldness, tachycardia and light headedness. More severe signs include coma, deteriorating consciousness, extensor posturing (decerebrate, decorticate rigidity and opisthotonus), generalized convulsions and shock (Warrell *et al*, 1990). In our series 11 patients (2.06%) had blood glucose levels less than 40 mg% at the time of admission and all were comatose. Of these 11 patients 4 had only hypoglycemia and became fully conscious after infusion of 25% dextrose, whereas the other 7 patients re-

mained unconscious because of associated cerebral malaria. Hypoglycemia has also been reported after oral quinine treatment on the 7th day of treatment, presented as severe convulsions and coma (Kochar *et al*, 1995).

Hyperpyrexia was present in 25% patients in our series and it was associated most commonly with cerebral malaria. This might contribute to further fetal loss and abortion in pregnant women. Many patients of algid malaria were also having hyperpyrexia not responding to tepid sponging.

Significant bleeding was observed in approximately 5% of adult patients with cerebral malaria (Phillips *et al*, 1986). In our series 51 patients (9.58%) had various bleeding disorders (Table 1). Consumption coagulopathy is usually of a low grade but in a small proportion of cases it may become clinically important (Warrell *et al*, 1990). Throm-bocytopenia is a feature of falciparum malaria and sometimes profound in patients with severe disease, but this is not consistent enough to be of prognostic significance (Phillips *et al*, 1986), although in our series 4 patients had platelet counts below 20,000/mm^3, of which 3 expired (the other contributory causes of death in these patients were shock due to heme-temesis in 2 and ARDS in one patient). Platelet survival is reduced in *Plasmodium falciparum* malaria (Warrell *et al*, 1990). Upper gastrointestinal endoscopy was done in 15 patients who were having hemetemesis. Erosion and congestion was found in the first part of the duodenum, the antral part of the stomach and lower end of the esophagus. However, in 3 patients no specific abnormality was detected. Biopsy of mucosa did not reveal any malarial parasites, whereas, earlier studies (Wilairatana *et al*, 1992) demonstrated parasites in gastric mucosa on histopathological examination.

Changes in behavior may occur in the early stages of complicated malaria causing excitement and mania followed by coma (Dhamija *et al*, 1991; Vietze, 1978). Agitation and confusion may develop in the patient during recovery from unconsciousness. Transient paranoid psychosis or delirium may sometimes follow the acute illness. In our study 11 (2.67%) patients had psychiatric symptoms during the course of illness. The two patients expired who had concomitant cerebral malaria and acute renal failure, while the rest of the patients recovered completely. In 3 patients psychiatric symptoms appeared only during high fever.

Hyperparasitemia is an important determinant of mortality in severe malaria (Stephen, 1992; Dhamija *et al*, 1991; Macpherson *et al*, 1985; Phillips *et al*, 1986). We did not take this parameter into consideration because our primary and secondary health care stations were managed by doctors and diagnosis and effective anti-malarial treatment was also instituted at that point. Our finding thus was not the actual record of parasitemia at the beginning of treatment and thus it was not compared with trend of mortality and morbidity.

It is generally agreed that during pregnancy women in endemic areas show an increased prevalence of malaria. The greatest risk of infection occurs in the second trimester (Warrell *et al*, 1990). A pregnant woman poses a threat to herself or to the fetus when she developes malaria (Stephen, 1992; Dhamija *et al*, 1991). In our series pregnant women with malaria were more prone to develop severe anemia, hypoglycemia, cerebral malaria and pulmonary edema compared to non pregnant women and these factors contribute to high mortality and morbidity (Warrell *et al*, 1990). The placenta appears to be a site of preferential parasite sequestration and development, which presumably interferes with transplacental delivery of nutrients to the fetus. Acute placental insufficiency is the net result and, in areas of unstable transmission where symptomatic disease in the mother is common, fetal distress is commonly undiagnosed and the mortality is high, as in our series.

In our series 51 (9.59%) patients had more than 3 types of pernicious syndromes at a time. The mortality in these patients was very high, to the tune of 82.35%. The combination of cerebral malaria, hyperpyrexia, acute renal failure, pulmonary edema and jaundice was the usual presentation.

Assessment and analysis of local malaria problems are a prerequisite for embarking on any control activity. An appropriate epidemiologic information system is therefore an essential part of a control program. Epidemiologic information should include not only morbidity and mortality data, but also information on underlying factors relating to the human population, the parasite, the vector, the ecosystem and the impact of malaria (WHO, 1993). This study of 532 cases of severe and complicated malaria may help us in improving the information flow regarding the trends of the disease in the region and thereby help in formulating a strategy

for future malaria control as per global strategy (WHO, 1993).

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