

## THE CLINICAL PATTERN AND COMPLICATIONS OF SEVERE MALARIA IN THE GIZAN REGION OF SAUDI ARABIA

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Malaria remains a major problem in many parts of the world. Approximately 500 million people are affected annually, and about three million, mostly children, die of falciparum malaria each year.<sup>1-5</sup> In areas of endemic malaria, the most common clinical presentation is that of uncomplicated infection with prompt recovery after treatment.<sup>6,7</sup> However, in nonimmune individuals, malaria may present in its most severe forms.<sup>2,5,6,8</sup>

Despite a vigorous program of malaria control in the Kingdom of Saudi Arabia, the infection is still endemic in the southwestern area of the country.<sup>9</sup> As a result of continued preventive measures, the epidemiology of the disease may be changing, and the proportion of non-immune individuals may increase. Furthermore, the emergence of chloroquine-resistant malaria in the neighboring country of Yemen has a major implication for the Gizan population.<sup>2,4</sup> The frequency and clinical outcome of severe malaria may provide useful, albeit indirect, information on the emergence of antimalarial drug resistance in this region. We describe the clinicopathologic profile and mortality in patients treated for severe malaria in King Fahad Central Hospital (KFCH), Gizan, Saudi Arabia.

### Materials and Methods

The Gizan region is one of the 14 administrative provinces of Saudi Arabia. It is located on the Red Sea coast, about 1000 km southwest of Riyadh, and shares its border with Yemen to the east, and the Asir region to the north. The population of about one million is distributed mainly in the rural areas. All serious and complicated cases from the various general hospitals in the region are referred to the KFCH, which is the regional referral center. In addition, the emergency room is open 24 hours each

day, allowing self-referral or presentation by those needing emergency care.

The medical records of all cases of malaria admitted to the KFCH, from 1995 to 1997 (a three-year period), were analyzed. Malaria was diagnosed by the clinical presentation of fever, positive blood smear for asexual forms of *Plasmodium falciparum*, and response to anti-malarial therapy. After a detailed history was obtained from either the patient or accompanying relatives, the patient was carefully examined. Thick and thin blood films were stained with Giemsa for the detection and characterization of malarial parasites. The parasite load was estimated to range from mild to severe on a scale of 1-4, corresponding approximately to <5%, 5%-10%, 10%-20%, and >20%, respectively. Additional investigations included the determination of hemoglobin level (Hb), white blood cell count (WBC), hematocrit, platelet count, reticulocyte count, mean corpuscular hemoglobin concentration, electrolytes, blood urea nitrogen (BUN), creatinine, blood glucose, bilirubin, aminotransferase, and lactic dehydrogenase in all the patients. Blood cultures, chest x-ray, abdominal ultrasound, urine and stool examination were done where indicated. Cerebrospinal fluid examination and CT scan of the brain were performed in some of the patients, as indicated clinically.

The malaria infection was considered severe in the presence of a relatively high density of parasitemia (more than 4/high-power field of erythrocytes parasitized by *P. falciparum*), or the presence of parasitemia and the association of severe manifestations and complications such as coma, convulsions, shock or severe anemia (hematocrit <20% or hemoglobin <50 g/L). Intravascular hemolysis (hemoglobinuria), hypoglycemia (glucose <2.2 mmol/L), renal impairment (serum creatinine >265 µmol/L), coagulopathy, acute respiratory distress syndrome and acidosis were all checked according to WHO guidelines.<sup>6</sup>

Cerebral malaria was diagnosed in the presence of alteration of consciousness, or an unarousable coma after all other causes were excluded. Patients were treated with antimalarial drugs (i.e., chloroquine, quinine, mefloquine or Fansidar®), and other supportive therapy (e.g., fluid replacement and blood transfusion, etc.).

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TABLE 1. Symptoms, signs and laboratory data in 246 cases of severe malaria in Gizan region, 1995-1997.

	Number (%)
<b>Symptoms</b>	
Fever	246 (100)
Chills/rigors	194 (78.8)
Headache	71 (28.8)
Vomiting	123 (50.0)
Dark urine	13 (5.2)
Diarrhea	13 (5.2)
<b>Signs</b>	
Pallor	97 (39.4)
Jaundice	58 (23.5)
Drowsiness	63 (25.6)
Hepatomegaly	53 (21.5)
Splenomegaly	64 (26.0)
Coma	24 (9.7)
Convulsions	24 (9.7)
<b>Laboratory abnormalities</b>	
Hemoglobin <50 g/L	42 (17.1)
Platelet count <100,000/mm <sup>3</sup>	124 (50.4)
WBC >10,000/mm <sup>3</sup>	63 (25.6)
LDH >200 IU/L	57 (23.1)
Hemoglobinuria	38 (15.4)
DIC	8 (3.2)
BUN >6 mmol/L	42 (17.0)
Creatinine >265 µmol/L	15 (6.1)
ALT >100 IU	17 (6.9)
Blood sugar <2.2 mmol/L	5 (2.0)

LDH=lactic dehydrogenase; DIC=disseminated intravascular coagulation; BUN=blood urea nitrogen.

TABLE 2. Frequency of complications in 246 patients with severe malaria in Gizan region, 1995-1997.

Complications	Alone (%)	Combined* (%)	Total (%)
Cerebral malaria	25 (10.0)	39 (15.8)	64 (26.0)
Thrombocytopenia	74 (30.0)	50 (20.3)	124 (50.4)
Acute renal failure	0	15 (6.1)	15 (6.1)
Intravascular hemolysis	11 (4.4)	27 (10.9)	38 (15.4)
Disseminated intravascular coagulopathy	0	8 (3.2)	8 (3.2)
Hypoglycemia	0	5 (2.0)	5 (2.0)
Acute respiratory distress syndrome	0	4 (1.6)	5 (1.6)

\*Occurrence with one or more other complications.

## Results

Of the 246 patients (154 males and 92 females) diagnosed with malaria in this study, 210 were Saudis and 36 were non-Saudis. The non-Saudi patients comprised 22 Yemenis, four Egyptians and 10 Asians. The age of the patients ranged from 8 months to 90 years, and 70.2% (185 of 246) were less than 30 years in age.

The history of fever was universally present, and in 78.8% of the cases it was associated with chills and rigors. Jaundice (23.5%), splenomegaly (26%), and hepatomegaly (21.5%) were the most common physical abnormalities (Table 1). Severe anemia (Hb<50 g/L) occurred in 42 (17.1%) and moderate anemia (Hb 50-89 g/L) was present in 104 patients (42.2%). Thrombocytopenia (platelet count <100,000/mm<sup>3</sup>) was present in 124 patients (50.4%), and

was significantly low (<50,000/mm<sup>3</sup>) in 41 (16.6%). Intravascular hemolysis with hemoglobinuria was diagnosed in 15.4% of cases (Table 1). The occurrence of two or more complications was observed in 44 patients (17.9%). Acute renal failure (ARF) did not occur as an isolated complication without the presence of one or more of the other major complications (Table 2). The duration of hospitalization varied from four days to two months, an average stay of one week. Seven patients (2.8%) died during the hospital admission. The complications and causes of death are summarized in Table 3.

## Discussion

Falciparum malaria is a predominantly pediatric problem in the southwestern region of Saudi Arabia.<sup>9</sup> During the three-year study period, a total of 33,183 cases of malaria were reported to the Ministry of Health in the Gizan region. Only patients with severe illness are referred to KFCH, and the patients described here represented malaria in its most severe form. The clinical features of severe malaria include the occurrence of cerebral malaria, severe anemia, convulsions, ARF, pulmonary edema, shock and spontaneous hypoglycemia.<sup>6</sup> These were observed with various frequencies among our patients.

The frequency of cerebral malaria, the most severe complication of *P. falciparum* infection, is associated with lower levels of malaria transmission and background immunity of the respective populations.<sup>10,11</sup> In the present study, it was a common but major complication occurring in 26% of the patients, and was a contributory factor in all seven deaths. Our finding is consistent with earlier reports in which cerebral malaria accounted for 80% of the deaths in malaria infection.<sup>1,2,6</sup>

Although 17% of our patients had elevated BUN, the occurrence of definite ARF (creatinine >265 µmol/L) was 6.1%, and the remaining cases were patients with pre-renal azotemia due to dehydration. This observation is in contrast with the reported frequency of 50% for significant renal impairment among patients with malaria.<sup>6,12</sup> Renal failure due to acute renal tubular necrosis is reported to be a major cause of death in severe malaria.<sup>6,8,12</sup> Three of our patients who died had ARF in association with other complications.

Hypoglycemia is commonly described in association with treatment of malaria with cinchona alkaloids (quinine or quinidine). These are potent stimulators of insulin secretion by the pancreatic B cells. Spontaneous hypoglycemia as a complication occurs most frequently in adults (particularly with pregnancy), and in children with very severe infection. In such cases, it may be the result of an increased glucose consumption due to fever, infection, aerobic glycolysis, and the metabolic demands of the parasites.<sup>4,8,13</sup> Only 2% of our patients had reversible hypoglycemia, and none of our six pregnant patients had this complication.

TABLE 3. Causes of mortality in 7 of 246 patients with severe malaria in Gizan region, 1995-1997.

Age/sex	Nationality	Cerebral malaria	Complications
30/F	Eritrean	+	Coma
28/M	Saudi	+	Acute renal failure, pneumonia
80/M	Saudi	+	Cardiorespiratory arrest
40/M	Indian	+	Acute renal failure, acute respiratory distress syndrome
5/M	Saudi	+	Coma
5/M	Saudi	+	Pneumonia, convulsions
41/M	Saudi	+	Acute renal failure, hypoglycemia, shock, disseminated intravascular coagulation

In this study, thrombocytopenia was the most common complication (50.4%). It has been suggested that the low platelets in malaria are due to sequestration in the spleen, rather than to the failure of production by the marrow or to immune-mediated lysis.<sup>4</sup> The thrombocytopenia reversed quickly on treatment, except in one patient who had evidence of disseminated intravascular coagulation (DIC). In areas of endemicity for viral hepatitis, the presentation of malaria with jaundice and fever may pose a diagnostic dilemma, particularly if hepatomegaly is present. About 30% of patients with malaria present with jaundice,<sup>4,6</sup> and this is comparable with the frequency of 23.5% in our patients. Jaundice is due to one or more factors, and these include intravascular hemolysis (observed in 15.4% of our patients), hepatic dysfunction (in 7%) and microangiopathic hemolysis associated with DIC (in 3%).

The availability of effective chemotherapeutic agents has resulted in early treatment of malaria in endemic areas, and has reduced the mortality rates where health care facilities are available and easily accessible. These factors may account for the low mortality (2.8%) among patients with severe malaria treated in our hospital.

In a retrospective analysis such as reported here, we were unable to evaluate the frequency of chloroquine-resistant malaria in the patients analyzed. The majority of patients were routinely treated with quinine on the basis of severity or presence of complications, rather than on proven chloroquine resistance. Saudi Arabia is categorized by the WHO to be in Zone A—countries in which *P. falciparum* is considered to be sensitive to chloroquine. However, recent reports suggest that chloroquine resistance may occur in some parts of Saudi Arabia.<sup>14,15</sup> In the Gizan region, Akood et al. of the Training and Research Center for Malaria performed *in vitro* testing on

97 isolates of *P. falciparum*, and found that 27 were resistant to chloroquine (personal communication). In this retrospective analysis, it was not possible to identify patients who might have been clinically resistant to chloroquine therapy. The frequency of chloroquine resistance among patients with severe malaria needs to be determined by well-designed prospective studies in the Gizan region.

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