Chloroquine-Resistant *Plasmodium falciparum* Cerebral Malaria in a Chloroquine-Susceptible Area

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Chloroquine-resistant *Plasmodium falciparum* is endemic in many areas. Saudi Arabia was considered to have chloroquine-susceptible *P. falciparum*. During the 1997–1998 season, an outbreak of malaria occurred in the southwestern region. Over a 4-month period, 32 cases (6.2%) of 520 malaria admissions met the World Health Organization criteria for cerebral malaria. The mean patient age was 28 years. Thirteen male and 19 female patients were admitted in coma. The mean duration of coma was 4.3 days; the case fatality rate was 41%. Compared with those who recovered, patients who died had a lower mean admission diastolic blood pressure and hemoglobin level, higher mean blood urea nitrogen and blood glucose levels, and thrombocytopenia. Logistic regression analysis identified treatment with quinine rather than chloroquine to be associated with survival. These findings show the potential of *P. falciparum* to emerge as chloroquine resistant in previously susceptible areas, resulting in significant morbidity and mortality in spite of sophisticated medical care.

About 40% of the world’s population is at risk of acquiring malaria. There are 300–500 million clinical cases annually, resulting in up to 2.7 million deaths [1]. Mortality is higher in children and nonimmune populations. Cerebral malaria is one of the complications of severe malaria that can result in a mortality rate as high as 50%. In Africa, about half a million children die annually from complications of cerebral malaria. Each year 25–30 million travelers from nontropical countries visit malaria-endemic areas [2]. Such travelers are at risk of acquiring chloroquine-resistant *Plasmodium falciparum*, which is endemic in many parts of the world. As recently as 1997, Saudi Arabia was considered to have chloroquine-susceptible *P. falciparum* [3]; 89% of the 20,000 cases reported annually are attributed to this organism. The majority of malaria cases are reported from the southwestern region of Jazan [4], with an increase in reported cases occurring during the rainy season between November and March. Care of patients with malaria is provided at the level of primary health care centers, with complicated cases being referred to the regional tertiary care hospital, King Fahad Central Hospital (KFCH) in Jazan. On average, 1–3 cases of cerebral malaria are referred annually to the regional hospital. During the season of 1997–1998, there was a significant increase in malaria cases in the region. This increase was associated with increased reports of chloroquine failure as therapy for malaria. We also noticed significant increases in cerebral malaria patients admitted to KFCH. We have collected data on all admissions with complicated malaria. The clinical presentation, outcome, and mortality risk for patients with cerebral malaria are presented in this report.

**Patients and Methods**

The World Health Organization (WHO) research diagnostic criteria for cerebral malaria were used to define a case of cerebral malaria among malaria admissions [5]. All of the following criteria have to be present: (1) unarousable coma, (2) exclusion of other encephalopathies, and (3) confirmation of *P. falciparum* infection by presence of asexual forms in blood smears.

Patients suspected of having cerebral malaria were tested by blood cultures, brain imaging, and cerebrospinal fluid (CSF) sampling for cytologic analysis and culture. Data collected from all patients admitted with malaria included demographic information, area of origin, parasitological data, clinical data on presentation, diagnostic evaluation, therapies, and outcome. Chloroquine was given as 10 mg base/kg for the first 2 days and 5 mg/kg on the third day. Quinine was given as 10 mg/kg every 8 h for 7 days in combination with tetracycline or clindamycin. Quinine dihydroc...
lroride therapy was started intravenously when the patients were admitted. Recommendations of the WHO for malaria therapy were adopted by the primary health care centers in the region.

Assessment of the response of \textit{P. falciparum} to chloroquine was done by use of the in vitro Micro-Test (MARK II) provided by the WHO. Patients who had blood films suggestive of \textit{P. falciparum} infection and who had received no antimalaria therapy as confirmed by urine screening were considered for in vitro testing. Blood was collected by finger prick in a heparinized capillary tube to a volume of 100 \( \mu \)L. Subsequent handling and incubation were as directed by the WHO manual for in vitro testing. Resistance to chloroquine was considered if schizont growth was noted at chloroquine concentrations of 8 pM or more.

Epi-Info version 6.04 (CDC, Atlanta, GA, and WHO, Geneva) was used for data collection. Statistical analysis was performed by use of SAS software (SAS Institute, Cary, NC). Student’s \( t \) test was used to compare continuous variables, and \( \chi^2 \) or Fisher’s exact test was used to compare proportions. All statistical tests were 2-tailed. A \( P \) value <.05 was considered statistically significant. Patients with cerebral malaria who survived were compared with nonsurvivors. Logistic regression analysis was used to assess the effect of independent variables on outcome in both groups.

\section*{Results}

Patients with clinical cases of malaria in Jazan were diagnosed and treated at 130 primary health care centers in the region. Patients with complicated cases who were admitted toKFCH for further management numbered 520. Between December 1997 and March 1998, 32 patients (6.2\%) met the WHO criteria for cerebral malaria. All patients were admitted to the intensive care unit. The 32 cases were not clustered in time or place. None of the patients had a history of blood transfusion or travel to an area known to have chloroquine-resistant \textit{P. falciparum}. They were all natives of the region and presented with clinical malaria for the first time. All blood and CSF cultures were negative. Mean age (\( \pm SD \)) was 28 \( \pm \) 26 years, the median age was 17 years (range, 1–80 years), 59\% were male, and 41\% were female. Ten (31\%) of the patients were children aged <12 years. Mortality in children (5/10) compared with adults (8/22) was not statistically significant (Fisher’s exact test, \( P = .7 \)). Thirteen patients (41\%) died. Table 1 summarizes the differences in clinical, laboratory, and treatment data between survivors and nonsurvivors. There was no statistically significant difference between the 2 groups in the mean age, mean duration of symptoms, area of origin, history of medical illness, mean duration of parasitemia, mean duration of hospitalization, or mean duration or scale of coma. Fifteen patients (47\%) did not receive antimalaria therapy before admission to KFCH. Mortality in this group (6/15) was not statistically different, compared with patients who had received some antimalaria therapy before admission. Pre-hospital admission chloroquine was given to 10 patients, 5 of whom died, compared with 2 deaths among the 7 patients who received oral quinine. The mean age, duration of symptoms, admission blood pressure, hemoglobin level, platelet count, creatinine and blood urea nitrogen levels, coma scale, and duration were not different in the chloroquine-treated population, compared with the quinine-treated population. Mean admission blood glucose level was lower in the quinine-treated population, but this difference was not statistically significant (6.8 vs. 9.1 mM/L, \( P = .07 \)). On admission, 28 of the 32 patients received intravenous quinine. The remaining 4 patients were admitted early in the outbreak and received chloroquine through a nasogastric tube. Three of them died.

There were few elderly patients, hence we noted elevated mean ages of 22 and 36 years for survivors and nonsurvivors, respectively (median ages were 15 and 32 years, respectively). The difference in mean admission platelet count was not statistically significant (\( P = .09 \)). However, 12 of the 13 patients who died were considered to have thrombocytopenia, defined as platelet count \(<100 \times 10^4/\mu L\), whereas 10 of the 19 surviving patients had thrombocytopenia (odds ratio, 10.8; \( P = .02 \)). Logistic regression analysis identified treatment with quinine alone as the only variable to have significant effect on survival (\( P = .03 \)). Among the parasites grown from clinical malaria and surveillance patients during the 1997–1998 season, 38\% were found to be resistant to chloroquine by use of in vitro Micro-Test (MARK II).

\begin{table}
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Variable & Nonsurvivors & Survivors & \( P \) \\
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\( \text{Age, years} \) & 36 \( \pm \) 32 & 22 \( \pm \) 19 & \( .1 \) \\
\( \text{Admission diastolic BP, mm Hg} \) & 55 \( \pm \) 16 & 67 \( \pm \) 9 & \( .02 \) \\
\( \text{Admission hemoglobin, g/L} \) & 58 \( \pm \) 38 & 99 \( \pm \) 21 & \( .001 \) \\
\( \text{Admission platelets, 10^9/L} \) & 67 \( \pm \) 62 & 134 \( \pm \) 124 & \( .09 \) \\
\( \text{Admission BUN, mM/L} \) & 20 \( \pm \) 14 & 8 \( \pm \) 8 & \( .01 \) \\
\( \text{Admission creatinine, mM/L} \) & 214 \( \pm \) 202 & 117 \( \pm \) 105 & \( .1 \) \\
\( \text{Admission glucose, mM/L} \) & 11.9 \( \pm \) 8 & 7.2 \( \pm \) 2 & \( .03 \) \\
\( \text{Hospitalization, days} \) & 5.2 \( \pm \) 5 & 9.3 \( \pm \) 7 & \( .1 \) \\
\( \text{Duration of parasitemia, days} \) & 2.3 \( \pm \) 1.6 & 3.0 \( \pm \) 1.1 & \( .2 \) \\
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\caption{Differences in clinical, laboratory, and treatment data between survivors and nonsurvivors of cerebral malaria.}
\end{table}

\section*{Discussion}

Reported malaria cases have been increasing worldwide. In Saudi Arabia, malaria control was successful in areas other than the southwestern region, which alone contributes >50\% of the reported cases nationally. The rate of malaria cases per 100,000 population in Jazan was more than 10 times higher than the national rate of 106 cases per 100,000 population in 1995 [4]. Over the last few years, malaria transmission has been stable. The number of cases and response to therapy were noted
to have changed early in the season of 1997–1998. More cases were reported, and chloroquine failure was noted frequently. Saudi Arabia is considered one of the few areas where *P. falciparum* remains sensitive to chloroquine [3]. However, there were some indications that chloroquine resistance may be emerging [6]. During the season of 1997–1998, the proportionate increase in cerebral malaria cases was higher than the proportionate increase in the total number of cases. The reason why some malaria patients develop cerebral malaria remains obscure. Several factors may have contributed to the outbreak, the increased number of cerebral malaria cases, and failure of chloroquine. The unusually high rainfall this season, following several years of below-average rainfall and subsequent relaxation in control measures, has resulted in increased vector population. The immunity of the population against malaria parasites is probably reduced after a few years of low transmission rates [4]. The increase in immigrant workers from neighboring Yemen, where chloroquine resistance is known to occur [3], may have introduced the chloroquine-resistant parasites. Secondary resistance of *P. falciparum* to chloroquine is known to evolve with inappropriate use of chloroquine.

In the 1999 edition of *International Travel and Health, Vaccination Requirements and Health Advice* from WHO, Saudi Arabia has 2 areas for malaria prophylaxis requirements. The southwestern region is designated area B, where prophylaxis with chloroquine and proguanil is recommended. For the rest of the country, designated area A, chloroquine prophylaxis is considered sufficient if required.

Several reports have addressed mortality risk factors in cerebral malaria [7–10]. These patients were usually children. In our series, only 31% of the patients were aged <12 years. Mortality was not statistically different between adults and children. The overall mortality was 41%, which is similar to that shown in other reports [11, 12]. However, given the short duration of symptoms and rapid access to an intensive care facility, the rate is still high. As reported by others, mortality was associated with anemia, renal impairment, thrombocytopenia, and use of chloroquine rather than quinine [7–10]. In addition, we noted lower diastolic blood pressure to be associated with mortality. The anemia remained a significant factor even after correcting for 2 patients with sickle cell disease in the mortality group. Other factors may have contributed to the high mortality rate, including parasite load, reduced immunity to *Plasmodium*, and older age. However, because of the small numbers, the statistical power may not have been enough to show a difference. In a multivariate analysis, lack of quinine therapy was the only factor associated with mortality. This finding and the in vitro chloroquine resistance rate of 38% point to the role of chloroquine resistance as a factor in this outbreak and the high rate of complications. Currently, chloroquine is not used as primary therapy for malaria in Jazan.

Although previous reports identified hypoglycemia as a risk factor for mortality in severe malaria [7], in our series mean admission blood glucose was significantly higher in patients who eventually died, even after adjustment for 2 elderly diabetic patients. There are several differences in our patient population that may explain this finding. The mean age of our patients (28 years) is higher than that in most reported series of cerebral malaria. The prevalence of diabetes mellitus in the native population is very high: 14% and up to 49% in older age groups [13]. Moreover, although the mean duration of symptoms and parasite load were the same in survivors and nonsurvivors, the survivors in our report had received more quinine, compared with nonsurvivors who received chloroquine. The role of quinine in reducing blood glucose levels in patients with malaria and healthy volunteers is well documented [14].

Similar outbreaks of severe malaria have been reported in the literature; Koch et al. described an outbreak of severe malaria in India [15]. Over a 4-month period in 1994, 532 patients with complicated malaria were admitted. Cerebral malaria cases accounted for 26% of admissions, the most common form of complicated malaria. Mortality in cerebral malaria was 34%. Again, increase in annual rainfall was one of the presumptive causes of the outbreak.

Our report emphasizes the role of *P. falciparum* as a parasite capable of emerging in an outbreak form with new antimicrobial resistance. In spite of rapid access to a sophisticated health care facility, cerebral malaria developed in several patients with resulting high case fatality rate. The implications of chloroquine resistance are not limited to therapy but also involve prophylaxis for travelers. Control measures should remain active even after several years of low malaria transmission. Cooperation and collaboration in control measures between neighboring countries will enhance chances for success of malaria control programs.

### References


