Original Article

Cerebral malaria in adult patients in the Sudan: Clinical presentation and outcome

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Abstract

Background
In endemic areas adults are less vulnerable to cerebral malaria (CM) than children because of acquisition of partial immunity. This prevalence difference is one of the reasons why we see fewer epidemiological and case studies in adult CM. The objective of this study was to determine the clinical presentation and outcome of CM in adult Sudanese patients.

Methods
A prospective hospital-based study was conducted in Khartoum Teaching Hospital. Thirty adult Sudanese patients presenting with CM conforming to the World Health Organization (WHO) definition of the disease were recruited. Their presenting features, laboratory investigations and clinical outcome were documented and studied.

Results
The mean age at presentation was 32.2 years ±15.4 SD. Nineteen patients (63.3%) were males and 11 (36.7%) were females. The predominant initial symptoms of CM were fever, excessive sweating, headache, nausea and vomiting. Before lapsing into coma, 15 patients (50%) manifested psychotic symptoms and 14 (46.7%) developed generalized convulsions. The neurological manifestations appeared after an average of six days from the onset of the febrile illness and reached its nadir within 24 hours. The level of coma was often deep, and 56.6% of patients had scored ≤3 in modified Glasgow coma scale. The case fatality was 23%.

Conclusion
CM was seen in all age groups. The classical febrile malaria paroxysms were not encountered. The majority of patients developed convulsions and/or psychosis before lapsing into coma. Mortality was higher in patients with modified Glasgow coma scale ≤3, and in those with ocular fundus findings.

Key words: cerebral malaria, clinical picture

Introduction
Malaria is still one of the major killing diseases. Two billion people, more than 40% of the world population in more than one hundred countries, live in the malaria endemic zone. There may be as many as 300-500 million infections per year, 90% in Africa(1,2). CM is the best known and the most frequent manifestation of severe falciparum malaria in adults in most parts of the world. In some reports CM accounts for about 10% of all cases of falciparum malaria admitted to hospital(3).

This study was conducted to describe the clinical presentation of CM in the adult Sudanese patients.
Material and Methods

Study area

The study was conducted in Khartoum Teaching Hospital, the largest referral hospital in the region, located in Khartoum the capital city of Sudan. The hospitals in Khartoum provide health service to the town dwellers and villagers in the surrounding suburban region, a population of over 5 million. The region has subsaharan hot climate with a seasonal rainfall. The winter months October - February are characterized by an outbreak of Plasmodium falciparum malaria due to peak transmission following the preceding rainy season July - September. Low-grade transmission and case incidence are maintained throughout the rest of the year.

Patients

Consecutive adult patients presenting with CM to the medical emergency department during the periods from 12 October 1998 to 15 November 1999 were recruited in this prospective study. The diagnosis of CM was made according to the World Health Organization definition\(^{(3-5)}\). The criteria included the presence of symptoms and signs of malaria, unarrousable coma of modified Glasgow coma scale \(\geq 7\), the presence of asexual form of plasmodium falciparum in the blood smears and the absence of other causes for the encephalopathy. If coma followed a generalized convulsion, it should last more than 30 minutes after the seizure. Patients who had other manifestation of severe malaria such as renal failure, pulmonary edema, hyperpyrexia, hypoglycemia, electrolyte disturbance and those with a history of alcohol or neuroleptic drug intake prior to presentation were excluded from the study. All patients were subjected to a thorough systemic and neurological physical examination. Informed consent was obtained in all cases from attending close relatives. The study was approved by the ethical committee of the Graduate Medical Studies Board of the Faculty of Medicine of the University of Khartoum.

Investigations

The following investigations were performed in all patients at presentation; Giemsa-stained thick and thin blood fields for the detection of Plasmodium spp, and parasite count\(^{(6)}\), full blood counts, blood glucose, urea and electrolytes, general urine analysis, liver function tests and serology for Salmonella and Brucella. Histocompatibility antigens and other genetic studies were not done. Lumbar puncture was performed in all patients and the cerebrospinal fluid was analyzed for cells, glucose, proteins and tested by enzyme linked immunosorbent assay for the encephalitic viruses; Herpes simplex, Measles, Mumps, Lymphocytic horiomeningitis, Varicella zoster, Human immunodeficiency, West Nile fever, Dengue fever and Rickettsia. All patients underwent cranial Computed tomography examination with and without contrast enhancement.

Data analysis

Information obtained was entered in a master flow chart and the data were analyzed using SPSS computer software.

Results

Thirty patients were included in the study. Their ages ranged between 16 and 70 years and the mean age was 32.2 years \(\pm\) 15.3 SD. Nineteen (63.3%) were male and 11 (36.7%) were females. All patients were residing in endemic areas and had experienced previous attacks of clinical malaria, however, none of them gave a history of a recent attack within
the last three months. Three patients gave a history of a previous episode of cerebral malaria. Sixty percent of patients had taken or started antimalaria medication before presentation.

**Clinical Features**

The patients were comatose when they presented, but most of them had had some preceding symptoms for 1-20 days (mean 6.7 ± 5.3 days) before coming to the emergency department. The commonest symptoms felt before losing consciousness were high fever, usually with a temperature above 40° C, associated with sweating, chills and rigors, nausea, vomiting and headache (Table 1).

### Table 1: Presenting clinical features in 30 adult patients with cerebral malaria

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Number affected (%)</th>
<th>Mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>28 (93.3%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>25 (83.3%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (86.7%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>21 (70%)</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>15 (50%)</td>
<td></td>
</tr>
<tr>
<td>Rigors</td>
<td>15 (50%)</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>15 (50%)</td>
<td></td>
</tr>
<tr>
<td>Convulsions</td>
<td>14 (46.7%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (30%)</td>
<td></td>
</tr>
<tr>
<td>Examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified GCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7 (23.3%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3 (10%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7 (23.3%)</td>
<td></td>
</tr>
<tr>
<td>Hypertonia /Hyperreflexia</td>
<td>8 (26.7%)</td>
<td></td>
</tr>
<tr>
<td>Absent abdominal reflexes</td>
<td>26 (86.7%)</td>
<td></td>
</tr>
<tr>
<td>Ocular fundus changes</td>
<td>8 (26.7%)</td>
<td></td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>7 (23.3%)</td>
<td></td>
</tr>
<tr>
<td>Opisthotonos</td>
<td>1 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>1 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>40.9 ± 10.7</td>
<td></td>
</tr>
<tr>
<td>Pulse rate/min</td>
<td>109 ± 16</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>120 ± 20</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>70 ± 15</td>
<td></td>
</tr>
</tbody>
</table>

More than two thirds of patients (46.7%) had generalized convulsions before lapsing into coma. Psychotic manifestations like hallucination and/or behavioral disorders such as confusion, agitation and aggression, poverty of talk, refusal of food and bed-wetting were seen in 40% of patients. Generalized convulsions followed psychosis in three patients (10%). Four patients (13.3%) did not show any premonitory cerebral symptom and directly went into coma. At presentation, the GCS assessment score ranged between 2 and 7 it reached its nadir within 24 hours of its onset. The level of coma was more often deep and in 56.6% of patients was ≤ 3 in GCS. Generalized convulsions were a common event during the coma state and it occurred in 18 patients.
(60%) and in 4 of them (13.3%) the seizures were recurrent.

High fever, pallor, dehydration, tachycardia and tachypnea were common observations at presentation. Isolated neck stiffness in the absence of any other features of meningeal irritation was seen in 7 patients (23.3%). One patient had bruxism, opisthotonus and decerebrate rigidity. Ocular fundal changes were seen in 8 patients (26.7%) commonly as papilloedema associated with retinal venous congestion and intravascular sludges. Isolated papilloedema or retinal vascular abnormalities could occur. Extensive flame-shaped retinal hemorrhages were rarely seen. Examination of extremities was unremarkable in most of the patients, but hypotonia, tendon jerk hyperreflexia and extensor plantar response was encountered in a few. Of interest, loss of superficial abdominal reflexes was almost a universal finding.

**Investigations**

Thick and thin blood films showed Plasmodium falciparum rings in all patients, and that was confirmed by the presence of positive nested PCR against the MSA-2 antigen of Plasmodium falciparum\(^7\) in all patients. Blood counts were normal apart from an occasional mild drop in hemoglobin concentration (mean 9.6 ± 2.4 g/dl). Random blood glucose level was normal in all patients. Routine blood chemistry and electrolytes were within normal limits except in one patient in whom the total serum bilirubin was 3.2 g/dl in the presence of normal liver enzymes. The Cerebrospinal fluid analysis for glucose, proteins and cytology did not reveal any abnormality. Serological screening for viruses was negative for all patients. All cranial computerized tomography scans were normal.

**Outcome**

All patients received intravenous quinine sulphate in 5% dextrose solution infusion starting with a loading dose of 20 mg/kg given over 4 h followed by a maintenance dose of 10 mg/kg 8 hourly for 7 days. The fever and other prodromal symptoms settled within 4 days and that was the first indication of a favorable response to treatment. Recovery from coma was noted, in average, 4 days after initiation of therapy. Twenty-two patients (73.3%) completely recovered and 7 died. Mortality was exclusively within the first 48 h. One patient developed post-malaria cerebellar ataxia.

**Discussion**

Cerebral Malaria is a well known potentially fatal complication of plasmodium falciparum infection. In endemic areas the disease is far less commonly encountered in the adult population than in children most likely due to acquisition of partial immunity induced by repeated exposure. Cerebral Malaria more often afflicts adults during seasonal malaria when the transmission is usually high\(^8\). Although adult patients constitute less than 10% of all cases of life threatening malaria in Africa, the mortality rate is higher and CM is the most common cause of death among them.

The disease was found to be twice as common in males when compared to females. That could be due to presence of undetermined sex related host factors, less exposure to mosquitoes or cultural behavior such as the nightly prolonged stay in dense perfumed smoke sauna exclusively used by women.

The predominant prodromal symptoms were fever, excessive sweating, severe headache, nausea and vomiting initially making CM indistinguishable from any other form of uncomplicated malaria. The classical
intermittent fever paroxysms were not seen, as these are not a feature typical of Plasmodium falciparum infection, and probably also because of early intake of antimalarial drugs by patients before presentation\(^3\).

The neuropsychiatric manifestations, mostly in the form of behavioral disturbances and epileptic convulsions occurred in just over half of the patients (53.3\%) within 4 days from the start of the prodromal symptoms and they usually preceded the loss of consciousness. When coma supervened, it tended to progress rapidly and reached its maximum depth within less than 24 hours.

In more than half of the patients the coma was deep with (GCS) score of \(\leq 3\). It is noteworthy that 6 of the 7 deaths, and the one who developed post-malaria cerebellar ataxia were all among those deeply comatose patients.

Vascular ocular fundus abnormalities with or without papilloedema, similar to our observation, were previously reported to be common in patients with CM\(^9\). The mechanisms of fundal changes are complex.

A histopathological study from Malawi had shown that sequestration of late-stage parasitized red blood cells with reduced amounts of hemoglobin accounted for the retinal vessel changes in CM\(^10\). Another study from Kenya suggested that hypoxia caused by “parasite metabolic steal phenomena” and nutritional deficiency rather than microvascular occlusion are the main underlying mechanisms. Other mechanisms suggested include toxic effect of cytokine or lactate released by parasites\(^11\). We observed that fundal changes only occurred in deeply comatose patients scoring \(\leq 3\) in GCS. That was consistent with previous observation that a deeper coma and specific ocular fundus findings were associated with poor outcome in patients with CM\(^3,9\). In our series we could not find a correlation between the level of coma and the time duration to recover from CM. Neck stiffness in the absence of other signs of meningeal irritation and absent superficial abdominal reflexes with preserved deep tendon and planter reflexes are recognized features in CM\(^3\).

History of previous episodes of CM was noted in three patients suggesting the presence of some form of susceptibility to disease progression in them. Host factors operating in determining mode of presentation and outcome of severe falciparum malaria are known to occur. In addition to the recognized inherited hemoglobin defects and structural abnormalities, at least three human genes of the major histocompatibility complex are identified and known to influence the outcome and presentation of malaria infections\(^12\). In an extension of this study we have studied the influence of humoral immune sub-class IgG response to P. falciparum, as another host factor, on the severity of clinical outcome in infected individual. We observed that IgG1 is significantly lower in patient with CM compared to uncomplicated malaria and to control\(^13\).

Parasite factors also play a role in development of CM in endemic areas. Shigidi et al studied parasite diversity in a Sudanese population and have shown that the development of CM in adults residing in endemic areas is more dependent on strain multiplicity rather than on a specific strain or strains of Plasmodium falciparum. They also showed that the parasite intensity has no co-relation to disease severity\(^14\).

Oral or parenteral Chloroquine are routinely prescribed for an acute attack of malaria in outpatient clinics or in health centers. Occasionally combined Sulfadoxine-
pyrimethamine tablets (Fansidar) are given instead, but the latter is more often given when symptoms persist after completing a chloroquine therapy. Sixty percent of our CM patients had received some form of antimalarial chemotherapy, commonly oral chloroquine, before coming to hospital. This reflects the magnitude of resistance of Plasmodium falciparum strains to chloroquine in our region\(^{(15)}\) and we advocate for the use of intravenous quinine as the first choice in treatment of all types of severe malaria.

In conclusion CM, though common in children, can affect all age groups. High mortality and ocular fundus changes are more common in deeply comatose patients who had modified GCS < 3. Special attention should be directed to individuals who have a previous history of CM when they get symptoms of a new infection since they are prone to develop the cerebral form.

References
خلاصة

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محمد ادريس
معاوية مختار
تاج الدين سكري

مقدمة: في الأماكن التي تسبطن فيها طفل الملايا يكتسب المستوطنون قدرًا من المناعة ضد المرض، ويكون هذا القدر من المناعة أكبر بكثير لدى البالغين من السكان بالمقارنة لرفاقهم من الأطفال، لذلك نجد أن حالات الملايا الدماغية وكذلك الدراسات الميدانية للمرض أكثر ندرة في مجموعات البالغين من السكان. هدف هذه الدراسة وصف حالات سودانيين مرضى بالملايا الدماغية عند أول حضورهم للطبيب ومعرفة سير ومصير المرض عند وبعد علاجهم

الطريقة: أجريت دراسة متابعة أية على ثلاثين من مرضى الملايا الدماغية البالغين في مستشفى الخرطوم التعليمي، وتم تحديد التشخيص المرضي حسب تعريف هيئة الصحة العالمية، ثم جمع المعلومات عن الوصف السريري والحوص المخبرية التي أجريت ثم أخذت لدراسة تحليلية

النتائج: شملت الدراسة 30 مريضًا؛ 19 (63.3%) من الذكور و11 (36.7%) من الإناث. متوسط العمر عند الحضور كان 32.2 ± 15 سنة. أكثر الأعراض شرعًا كانت الحمى والتعرق والصداع والتعب والفيزيو. 15 (50%) مريضا أظهرا أعراض نسبية و14 (46.7%) أصيبوا بالتشنجات المصرفية العامة، وذلك قبل قِسطهم لوع. ظهرت الأعراض العصبية بعد 6 أيام في المتوسط بعد حلول الحمى، وبلغت الأعراض فمة شديدة خلال 48 ساعة. كانت الغثيان في معظم الحالات عنيفة وبلغت 3/3 في مقياس جلاسكو معدل في 62.9% من المرضى

خاتمة: تسبب الملايا الدماغية جميع الأمراض ولكن عند البالغين قد لا تظهر الحمى النمطية الدورية الشديدة، معظم المرضى يصابون بالتشنجات أو الأعراض النفسية قبل قِسطهم لوع. نسبة الوفاة عالية عند الذين بلغت حدة الاعتماد لديهم 3 في مقياس جلاسكو معدل أو ظهرت لهم تغيرات مرضية في قاع العين.