Seizures and status epilepticus in childhood cerebral malaria

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Summary

Prolonged, multiple seizures complicate a high proportion of cases of childhood cerebral malaria, and several studies have shown an association between these and neurological sequelae. We prospectively studied 65 patients (38 female) admitted to Kilifi Hospital in 1994. Electroencephalographic recordings (EEGs) were made at 12-hourly intervals, with continuous recordings made on a cerebral function analysing monitor (CFAM). Survivors were seen one month after discharge. Cerebral computerized tomography was performed on children with neurological sequelae. Sixty-two percent of patients had seizures following admission, of whom half had an episode of status epilepticus. Fifty-two percent of seizures were partial motor, 34% generalized tonic-clonic, and 14% partial with secondary generalization. In 22%, coma appeared to be due to a prolonged postictal state. Ten children had subtle motor seizures. Posterior parieto-temporal discharges were the most common EEG finding. Seven children died, eight developed neurological sequelae, and 50 (77%) recovered fully. Status epilepticus was associated with the development of neurological sequelae. Prolonged, multiple seizures may play an important part in the pathogenesis of coma in childhood cerebral malaria, and are likely to contribute to both the morbidity and mortality of this disease.

Introduction

Malaria is a major cause of morbidity and mortality in sub-Saharan Africa, causing the death of over one million children each year.¹ Approximately 1% of clinical infections with Plasmodium falciparum result in severe disease, of which one of the most serious forms is cerebral malaria,¹,² with a mortality of 10–40%.³,⁴ Although most survivors make a full recovery, neurological sequelae (hemiplegia, speech problems, cortical blindness, epilepsy) occur in 5–15%.⁵,⁶

Although the cause of coma in cerebral malaria is not known, the essential pathological feature is sequestration of parasitized red blood cells in the cerebral microvasculature.⁷ Neuronal damage may result from interference with microcirculatory flow and consequent hypoxia, intracranial hypertension secondary to increased cerebral blood volume,⁸ or the local release of toxic mediators such as cytokines, nitric oxide and excitotoxins neurotransmitters.⁹,¹⁰ Patients present with a diffuse encephalopathy, and seizures, which are often prolonged and multiple, occur in up to 80% of cases.³,¹ⁱ,¹² Uncontrolled seizure activity can damage the brain by aggravating hypoxia, hypoglycaemia and intracranial hypertension,¹³ and several studies have suggested an association between status epilepticus and neurological sequelae in childhood cerebral malaria.⁵,⁶

Despite their high prevalence and potential pathogenic importance, there have been no detailed studies of seizures in cerebral malaria. Here we describe the clinical and electrophysiological spectrum of seizures in childhood cerebral malaria in an area of Kenya where malaria is endemic.
Methods

Study site

The study was conducted on the 5-bed KEMRI paediatric research ward at Kilifi District Hospital, Kilifi, Kenya, between January and September 1994. The characteristics of malaria transmission and the population from which patients were drawn have been described previously.14

Patients

Children aged 9 months and above were eligible for enrolment in the study if they fulfilled the World Health Organisation (WHO) definition of cerebral malaria, namely unrousable coma not attributable to any other cause in the presence of asexual Plasmodium falciparum parasitaemia.15 To fulfil the definition of cerebral malaria, coma had to persist for at least 1 h after a seizure and/or after the administration of diazepam. Depth of coma was quantified using the Blantyre coma score,3 in which a coma score of 5 denotes full consciousness, and 0 complete absence of any response to painful stimulus. One hundred and ten children who fulfilled this definition of cerebral malaria were admitted during the study period. Sixty-five (60%) were recruited, since for technical reasons it was only possible to study two children at a time.

Clinical investigations and management

A clinical history and complete physical examination was performed on all children. Blood was taken for baseline assessment of parasite count, full blood count, urea and electrolytes, glucose, lactate, blood gas, and plasma chloroquine level. Electroencephalographic (EEG) recordings were made on a 14-channel Medelec 1A94 EEG machine. Silver/silver chloride electrodes were fixed with Elefix and tape to the child’s shaved head, and the International 10-20 system was used for electrode placement. Recordings were taken within 6 h of admission, and at 12-h intervals until recovery of consciousness (Blantyre coma score 5). Continuous recordings using a CFAM (cerebral function analysing monitor, Medaid Ltd) were obtained from children unconscious for more than 24 h. Any unusual neurological signs or witnessed seizure activity were recorded on video. In deeply comatose children, intracranial pressure was monitored using a subarachnoid catheter (Camino 110-4B). Intracranial hypertension is a feature of childhood cerebral malaria and, to reduce the risk of transtentorial herniation, lumbar puncture was performed once the clinical condition of the child had improved, or was done post-mortem in those who died. Children received standard antimalarial treatment with intravenous quinine 20 mg/kg loading dose and 10 mg/kg 8-hourly, or intramuscular artemether 3.2 mg/kg loading dose and 1.6 mg/kg every 24 h, as part of a multicentre study comparing the efficacy of quinine and artemether in the treatment of childhood cerebral malaria. Intravenous benzyl penicillin and chloramphenicol were administered until the results of lumbar puncture were known. Intravenous fluids and blood were given as clinically indicated. Seizures lasting more than 5 min were treated with intravenous diazepam 0.3 mg/kg. Recurrent (>3) seizures were treated with a loading dose of intravenous phenytoin 18 mg/kg and, if that failed, with intramuscular phenobarbitone 18 mg/kg. Children with continuous seizure activity lasting for 30 min or more were considered to have status epilepticus.16

Follow-up

All survivors were seen one month after discharge for neurological examination and repeat EEG. Cerebral computerized tomography (CT) was performed on all children with neurological sequelae.

Analysis

EEGs were analysed by SS who knew the age of each child, but was blind to any other clinical information. Statistical analysis was carried out using SPSS (version 5.0; 1992). Analysis of variance and Student’s t test were used to compare means of normally distributed data. Data not conforming to a normal distribution were compared by analysis of variance after logarithmic transformation, or by the Mann-Whitney U test. Proportions were compared by the \( \chi^2 \) test.

Results

Sixty-five children were studied, of whom 38 were female. Ages ranged from 9 months to 11 years (median 30 months). All had previously normal development. Children were unconscious for between 1 and 72 h (median 7 h) prior to admission. In over half the cases, onset of coma coincided with the onset of epileptic seizures.

On admission

Presenting clinical features and investigations are shown in Tables 1 and 2. Seventy-five percent of the children were deeply unconscious on admission, with a Blantyre coma score of 2 or less. Thirteen children (20%) had received diazepam on or up to 6 h prior to admission, in doses of between 0.2–1 mg/kg. In five cases, diazepam had been given
Seizures and cerebral malaria

Table 1  Clinical comparison of children with and without seizures after admission (n=65)

<table>
<thead>
<tr>
<th></th>
<th>No seizures after admission (n=25)</th>
<th>Partial seizures (n=28)</th>
<th>Generalized seizures (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)*</td>
<td>38.5 (29.9–47.1)</td>
<td>26.7 (20.6–32.9)</td>
<td>64.0 (44.7–83.5)</td>
</tr>
<tr>
<td>Past history of febrile seizures</td>
<td>2 (8%)</td>
<td>5 (18%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Pre-admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any seizures</td>
<td>15 (60%)</td>
<td>22 (78%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>11 (44%)</td>
<td>13 (46%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Admission coma score**</td>
<td>2 (2–3)</td>
<td>2 (1–4)</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>Admission temperature (°C)</td>
<td>38.8 (38.3–39.3)</td>
<td>38.4 (38.0–38.8)</td>
<td>39.4 (38.4–40.5)</td>
</tr>
<tr>
<td>Status epilepticus after admission</td>
<td>–</td>
<td>14 (50%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Neurological sequelae</td>
<td>3 (12%)</td>
<td>4 (14%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (16%)</td>
<td>2 (7%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

Data expressed as frequency (proportion) or mean (95% CI).
* p<0.001 for comparison between the three groups. For all other variables there was no statistically significant difference at the 5% level.
** Admission coma score expressed as median (range).

Table 2  Laboratory parameters on admission: comparison of children with and without seizures after admission (n=65)

<table>
<thead>
<tr>
<th></th>
<th>No seizures post-admission (n=25)</th>
<th>Seizures post-admission (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasitaemia (per µl)*</td>
<td>41523 (15306–112645)*</td>
<td>44846 (22315–90129)*</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>7.0 (6.1–7.9)</td>
<td>6.8 (5.8–7.7)</td>
</tr>
<tr>
<td>Na (mmol/l)</td>
<td>137 (133–140)</td>
<td>136 (134–137)</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>4.4 (4.0–4.8)</td>
<td>4.4 (4.1–4.7)</td>
</tr>
<tr>
<td>Urea (mmol/l)*</td>
<td>4.8 (3.2–7.2)*</td>
<td>4.7 (3.7–6.0)*</td>
</tr>
<tr>
<td>Creatinine (µmol/l)*</td>
<td>68 (54–86)*</td>
<td>54 (45–66)*</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.4 (3.5–5.3)</td>
<td>5.9 (4.6–7.2)</td>
</tr>
<tr>
<td>Corrected calcium (mmol/l)</td>
<td>2.05 (1.95–2.15)</td>
<td>2.10 (2.02–2.18)</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 (7.32–7.40)</td>
<td>7.32 (7.28–7.36)</td>
</tr>
<tr>
<td>Base excess</td>
<td>−7.3 (−10.7 to −0.9)</td>
<td>−7.2 (−9.7 to −4.7)</td>
</tr>
<tr>
<td>Lactate (mmol/l)*</td>
<td>3.3 (2.4–4.7)*</td>
<td>4.0 (3.1–5.0)*</td>
</tr>
<tr>
<td>Osmolality (mOsmol/kg)</td>
<td>289 (279–299)</td>
<td>289 (284–294)</td>
</tr>
<tr>
<td>Chloroquine (ng/ml of free base)**</td>
<td>80 (0–1570)**</td>
<td>43 (0–902)**</td>
</tr>
</tbody>
</table>

Data expressed as means (95% CI).
* Geometric mean (95% CI).
** Median (range); n=54, of whom 38 (70%) had detectable levels of plasma chloroquine. There were no statistically significant differences at the 5% level between the two groups for any of the above variables.

Intramuscularly at a health centre. Fourteen children (22%) had multiple seizures or status epilepticus on or immediately prior to recruitment, but had regained consciousness within 6 h of cessation of seizure activity.

Clinical course

Forty children (62%) had between one and more than 20 clinical seizures (median five), of duration 0.5–600 min (median 3 min). Eighteen children (28%) had one or more episodes of status epilepticus. Seventy-six percent of all seizures occurred within 24 h of admission. Fifty-two percent of the seizures were partial motor, 14% partial with secondary generalization, and 34% generalized tonic-clonic. Three children had both partial and generalized seizures during their clinical course. Partial seizures were slightly (64%), but not significantly, more common on the right side of the body. Only 42% of the 310 seizures documented were associated with a rectal temperature of 38 °C or above. Two were associated with hypoglycaemia. Ten children (25% of those with seizures after admission), with a median age of 26 months (range 9–60), had seizures that were clinically very subtle. In nine children these consisted of nystagmoid eye movements, salivation, and shallow, irregular respiration with concurrent hypoxaemia (arterial oxygen saturation below 80%) and hypercarbia (pCO₂ > 6.5 kPa). Although EEGs revealed continuous unilateral spike-wave discharges in the parieto-temporal region, sometimes
spreading to involve the whole of that hemisphere, there were either no manifestations in the contralateral limbs, or intermittent minimal clonic movements of a digit, eyebrow, or mouth. One child was admitted in deep coma, with irregular respiration, priapism, and salivation, following 6 h of generalized status epilepticus at home. EEG revealed generalized seizure activity, yet there were no other clinical accompaniments.

Twenty-six children received between one and five doses of intravenous diazepam, 0.3 mg/kg. In the majority of cases, cessation of clinical seizures occurred within 5 min of drug administration. In eight children, electrographic seizure activity persisted for between 2 and 140 min despite cessation of the clinical seizure with treatment. Intravenous phenytoin 18 mg/kg was given to 24 children, of whom 63% had no further seizures. Two out of four children who received intramuscular phenobarbitone also had no further seizure activity. In one child, intravenous thiopentone 4 mg/kg was effective at stopping generalized status epilepticus that had been unresponsive to three doses of diazepam and 18 mg/kg of both phenytoin and phenobarbitone.

Intracranial pressure (ICP) was monitored in 10 children, of whom four had a total of 31 (range 1–16) seizures during the course of monitoring. Both generalized and partial seizures caused a rise in intracranial pressure, the median rise in ICP (+164%, range 108–285) being greater during 18 generalized seizures than during 13 partial seizures (+50%, range 0–186). The magnitude of the rise was not affected by seizure duration. In all cases, a concurrent rise in mean arterial pressure meant that cerebral perfusion pressure was adequately maintained above 50 mmHg. Generally, intracranial pressure fell at the end of each seizure, but remained high (above 30 mmHg) for 2 min following the cessation of one generalized seizure. One period of electrographic seizure activity with no associated clinical manifestations was not associated with a significant rise in intracranial pressure.

**Electrophysiology**

Two hundred and seventy EEG and 30 CFAM recordings were made. During coma, the EEG was dominated by high-amplitude slow waves (4 Hz and below). Fifteen of 28 children with partial seizures had an EEG recorded during a clinical seizure. In all cases, ictal spike-wave discharges arose from the posterior parieto-temporal region (Figure 1). In eight of these cases there was considerable disparity between clinical and electrical seizure activity, with electrical activity spreading to involve all of one or both hemispheres despite the clinical seizure remaining partial. A further eight recordings from seven children with generalized seizures showed generalized ictal discharges. All children who made a full recovery had normal EEGs at one month follow-up.

**Outcome**

Fifty children (77%) made a full recovery, seven (11%) children died, and eight (12%) had persistent neurological sequelae one month after discharge. Among survivors, median time to localize a painful stimulus was 21.5 h (range 4–111 h). Of the eight children with sequelae, four had a hemiplegia, two had spastic quadriplegia, one had severe cognitive and speech problems, and one had epilepsy. The children with sequelae were significantly (p = 0.02) younger (mean age 20.4 months, 95% CI 6.2–34.5 months) than those who recovered fully (39.8 months, 95% CI 33.2–46.3 months). Six (75%) had status epilepticus before or after admission, as did 27 (54%) normal survivors. Two children who developed a spastic quadriplegia had severe hypernatraemic dehydration on admission. There were otherwise no significant differences in clinical or laboratory parameters between those with sequelae and normal survivors, but numbers are small. Seven of the eight children with sequelae had CT scans at one month follow-up and, with the exception of the scan from the child with epilepsy, all showed abnormalities. Scans from 3/4 children with hemiplegia revealed an area of infarction in the contralateral posterior parieto-temporal region (Figure 2). During their clinical course in hospital, two of these children had developed partial status epilepticus with electrical discharges arising from the same area. One child with partial motor status epilepticus and subsequent hemiplegia failed to attend for CT scan. CT scans on the two children with spastic quadriplegia and one with profound cognitive and speech problems showed generalized cerebral atrophy. Follow-up EEGs from children with residual hemiplegia showed low-amplitude slow wave activity in the contralateral parieto-temporal region, while EEGs from children with spastic quadriplegia were featureless and of low amplitude. Two (29%) of the seven children who died had status epilepticus during their clinical course. Those who died were significantly more acidic on admission (p values 0.04 and 0.01 for pH and base excess, respectively) than those who survived. One had *Haemophilus influenzae* septicaemia (but normal cerebrospinal fluid) and three had one or more episodes of hypoglycaemia. Laboratory parameters were otherwise unremarkable.

**Discussion**

The WHO definition of cerebral malaria attempts to delineate a homogenous encephalopathic syndrome
Figure 1. Continuous electrographic discharge over the left posterior temporal/occipital region. Clinical manifestations of the seizure were confined to nystagmus and eye deviation to the right.

associated with high levels of morbidity and mortality. Our data suggest that, in a proportion of cases, recurrent seizures play an important role in the pathogenesis of coma. Eighty-five percent of children in this series had at least one seizure during their clinical course, with the onset of coma associated with seizures in over half the cases. For the 22% who regained consciousness within 6 h of admission, coma appeared to result from prolonged or repeated seizures, and these children are likely to represent a different pathophysiological entity from those with prolonged coma. Following a prolonged seizure, the brain enters a phase of ‘cortical exhaustion’, with depletion of adenosine triphosphate, glucose, oxygen and the accumulation of lactic acid. In the postictal phase the EEG may be flattened, or show diffuse slow wave activity, the duration of the postictal phase being increased after prolonged or multiple seizures.

This study has also shown that in a proportion of children with cerebral malaria, coma is due to continuing subtle seizure activity which is likely to go undetected, but which is responsive to anticonvulsant drugs. Ten children (25% of those with seizures on or after admission) had seizures with minimal clinical manifestations, a recognized feature of prolonged generalized status epilepticus. The important point here is that the ictal features would be easily missed unless specifically looked for, yet uncontrolled seizure activity can damage the brain. Increased cerebral metabolism and hypercapnia both cause an increase in cerebral blood flow and therefore cerebral blood volume, so potentially exacerbating the intracranial hypertension that can complicate cerebral malaria. Subtle seizures are an easily treated cause of coma, and five of these children regained consciousness within 6 h of treatment with intravenous diazepam. Most children with cerebral malaria are admitted to busy, understaffed hospitals in the developing world, where subtle seizures are likely to be missed unless health personnel are trained in their detection.

What are the possible causes of seizures in cerebral malaria? Fever is known to precipitate seizures in young children. However, more than half the seizures documented after admission occurred when the rectal temperature was below 38 °C. Hypoglycaemia and electrolyte imbalance can cause seizures, yet only two seizures were associated with a blood glucose <2.2 mmol/l. It is likely that hypernatraemic dehydration was partly responsible for the status epilepticus and subsequent spastic quadriplegia that developed in two children. Although mild hyponatraemia and hypocalcaemia occurred in a
Figure 2. Cerebral CT scan obtained one month after discharge, showing extensive areas of infarction (numbered 1 and 2) in the left posterior temporal/occipital region, with associated cerebral atrophy. This 9-month-old child had multiple right partial motor seizures (including several episodes of status epilepticus) during her clinical course, and subsequently developed a dense right hemiplegia.

A proportion of children in this study, neither were significantly associated with seizures. Very high doses (plasma levels >2000 ng/ml) of chloroquine are known to cause seizures, but even low prophylactic doses can exacerbate seizures in an individual with a personal or family history of epilepsy. It is difficult to draw any firm conclusions from the chloroquine data presented in this study, since numbers are small and the timing, dose, and route of chloroquine administration are unknown. Four out of five (80%) children with plasma chloroquine levels of >400 ng/ml had seizures after admission, as did nine (56%) out of 16 children with undetectable chloroquine levels.

The characteristic histopathological feature of cerebral malaria is intense sequestration of parasitized red blood cells in the cerebral microvasculature. This suggests that local interference with blood flow could lead to seizures, either directly as a result of hypoxia, or by initiating the release of excitotoxic mediators such as glutamate or quinolinic acid. However, whilst sequestration appears to be a global phenomenon, the majority of patients in this study had partial seizures. Electrographically, these seizures were associated with ictal spike-wave activity in the posterior parieto-temporal region. This is a 'watershed' area, lying between territories supplied by the posterior and middle cerebral arteries. It is therefore particularly vulnerable to ischaemia when oxygen delivery to the brain is compromised as a possible result of severe anaemia, or inadequate cerebral blood flow due to hypotension, raised intracranial pressure or impaired autoregulation. CT scans on two children with partial seizures and subsequent hemiplegia showed infarction in this area. Although it is difficult to know whether the seizures caused infarction or vice versa, it is clear that uncontrolled seizure activity, with the concomitant increased demand for oxygen and glucose, is likely to exacerbate the situation.

Several studies of cerebral malaria have shown an association between status epilepticus and neurological sequelae, which occur in 5–15% of survivors. There is a large clinical and experimental literature to support the hypothesis that prolonged seizure activity can damage the brain, causing deficits in both motor and cognitive function. The hippocampus, which plays an important role in short- and long-term memory, is particularly prone to seizure-induced damage. The gross neurological sequelae described in this and other studies of cerebral malaria are likely to represent one end of a spectrum of a much wider range of handicaps. Many 'normal' survivors of cerebral malaria may have significant cognitive problems, with serious implications for their subsequent educational potential.

Can anticonvulsant prophylaxis reduce the incidence of status epilepticus complicating cerebral malaria? An ideal candidate drug would need to be cheap, safe, effective, and preferably administered by the intramuscular route. Phenobarbitone fulfils these criteria, yet its role in seizure prophylaxis in cerebral malaria is unclear, since two small published studies have produced somewhat conflicting results. If prophylactic phenobarbitone can reduce the incidence of status epilepticus complicating cerebral malaria, it is possible that this will also have an impact on the incidence of subsequent neurological sequelae. A definitive study of intramuscular phenobarbitone would therefore seem to be an important next step.

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References