Seizures in children with acute falciparum malaria: risk factors, mechanisms of neuronal damage and neuro-protection
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Chapter 6

Decorticate, decerebrate and opisthotonic posturing and seizures in Kenyan children with cerebral malaria

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ABSTRACT

Background
Seizures are a common feature of cerebral malaria in children and multiple seizures are a risk factor for poor outcome. Continuous electroencephalogram (EEG) recordings in comatose patients in intensive care units have demonstrated a high incidence of non-convulsive seizures that may damage neurons. The aim of this study was to describe electrographic characteristics of children with cerebral malaria detected with continuous EEG monitoring, compare the detection of seizures by clinical staff with that using continuous EEG, and relate specific EEG features to outcome.

Methods
Fifty-two children with cerebral malaria of whom, 38 were part of a randomized trial of fosphenytoin for prevention of seizures in acute non-traumatic coma, were prospectively enrolled on admission to hospital to undergo continuous EEG monitoring. Clinical seizures were recorded on a standard proforma that included the duration, type and manifestation of the seizures and interventions performed. The EEG recordings were analyzed by at least 2 clinicians and non-congruent results re-examined. At discharge, neurological assessment was performed to detect neurological deficits.

Results
The background EEG was characterized by very slow generalized high amplitude waves. A total of 372 seizures (149[40%] electroclinical and 223[60%] electrographic) were detected in 20/52 (38.5%) children. Most seizures were observed in 7 children admitted with status epilepticus. The majority had a focal origin but seizures involving a whole hemisphere were common among seven children with status epilepticus. A higher frequency of the background EEG was associated with a shorter duration of coma while an asymmetrical background EEG, rhythmic runs and electrographic status epilepticus were associated with death or neurological deficits.

Conclusion
Children with cerebral malaria and convulsive status epilepticus experience a big burden of electrographic seizures and electrographic status epilepticus is associated with poor outcome. Continuous EEG monitoring is a useful tool for the detection of such seizures and the acute EEG may be of prognostic value.
INTRODUCTION

Cerebral malaria is the leading cause of acute non-traumatic coma in tropical countries and the most severe neurological complication of infection with *Plasmodium falciparum*. It is associated with a high mortality and among survivors, up to 24% may have long-term neurological and cognitive deficits[1-3].

Seizures are a common feature of childhood cerebral malaria. Over 80% of children have a history of convulsive seizures on admission and 60% continue to have seizures after admission[4-6]. Recurrent and prolonged seizures are a risk factor for poor outcome (reviewed in [7]). These seizures may manifest as single convulsions, convulsive status epilepticus, subtle seizures or electrographic seizures detectable by electroencephalographic (EEG) monitoring. In a prospective observational study of serial EEG recordings of children with cerebral malaria in our unit, subtle and electrographic seizures were described in 15 out of 65 patients[8].

Recent studies of continuous EEG recordings among comatose patients in intensive care units have demonstrated a higher incidence of seizure episodes and in particular, subtle and electrographic seizures than on clinical observation alone[9-12]. These non-convulsive seizures may have damaging effect on neurons similar to the clinically observed convulsive seizures. Continuous EEG monitoring may improve their detection, provide insight into the pathophysiology of disease, and guide prognosis[13]. Other than the Kenyan study, which relied on data from serial EEGs, the frequency and electrophysiological characteristics of seizures in children with cerebral malaria has not been described.

We carried out prospective observations on continuous EEG recordings to describe the types and the electrographic characteristics of seizures in children with cerebral malaria, estimate the frequency of seizures, compare seizure detection by clinical staff with detection using continuous EEG, and relate specific EEG features to the clinical course of the disease.

METHODS

Setting

The study was conducted in the high dependency ward of Kilifi district hospital, coastal Kenya. This hospital admits approximately 5000 children aged 0-13 years annually of...
whom, 15% are treated in the high dependency unit. Between 100 and 150 children are admitted with coma.

**Study participants**

The study participants were children with cerebral malaria, aged between 9 months and 13 years. Cerebral malaria was defined as coma (inability to localize a painful stimulus [Blantyre coma score (BCS) ≤2]) at least 30 minutes after treatment of seizures or correction of hypoglycemia if present, with asexual forms of *Plasmodium falciparum* parasites on Giemsa stained peripheral blood smears and no other cause to explain the coma (in particular pyogenic meningitis). Patients with epilepsy, developmental delay, cerebral palsy, and sickle cell disease were excluded. Most of the study participants were part of a randomized placebo controlled trial of fosphenytoin for prevention of seizures and neuro-cognitive impairments in children with acute non-traumatic coma (ISRCTN11862726). Only half of the children who were eligible for this study between December 2004 and March 2006 underwent continuous EEG monitoring as per the trial protocol. Thereafter, continuous EEG monitoring was performed on all eligible and consented patients until March 2007. The Kenya Medical Research Institute Scientific and Ethical committees approved the study.

**Emergency care**

At admission, patients received emergency care based on standard guidelines[14]. Anticonvulsants were administered for all seizures at admission and for convulsive seizures lasting longer than 5 minutes after admission. This entailed a sequential administration of Diazepam (0.3mg/kg intravenously) or Paraldehyde (0.4mls/kg intramuscularly) as first line therapy. First line drugs were repeated if seizures did not stop within 10 minutes. Phenoobarbital (15mg/kg infused over 20 minutes) was administered for status epilepticus and sodium valproate (25 mg/kg infused over 20 minutes) was administered for refractory status epilepticus. Children with electrographic status epilepticus received similar treatment. Lumbar puncture was performed in the absence of features of raised intracranial pressure (ICP) or when patients regained a BCS greater than 2. All patients received intravenous Benzyl penicillin and chloramphenicol (for pyogenic meningitis) and quinine (for cerebral malaria) pending confirmation of diagnosis. Acyclovir is unavailable for routine use in this hospital. Antibiotics were discontinued when bacteremia and pyogenic meningitis were excluded.

** Acquisition and analysis of EEG data**

After stabilization, consent was obtained and patients set up for continuous EEG monitoring. Two patients were allocated sequentially to a 16-lead Nervus EEG monitor
(Taugagreining hf, Study room version 3.3.779, Iceland) for each child on a 21 lead video EEG machine (Grass-Telefactor Twin, Astro-Med [UK] version 3.4.57). Silver/silver chloride electrodes were applied to the child’s unshaved head with Elefix after cleaning with an abrasive gel and secured with colloidon and taped. The international 10-20 system was used for electrode placement[15]. EEG monitoring was performed till when the child regained full consciousness or for a maximum of 72 hours. Patients were closely monitored by the nursing staff and all seizure events recorded on a seizure monitoring chart stating the type and region of seizure onset and offset, the time, trans-cutaneous oxygen saturation, respiratory and heart rates at seizure onset and offset, blood glucose level and the interventions performed. These seizure events were classified as clinical seizures. The average patient to nurse ratio in the high dependency unit was 3:1.

Using pilot data from 16 patients, a standard proforma was developed and used for the analysis of EEG recordings. It included the background EEG activity at the start and end of recording, wave symmetry over the 2 hemispheres, region of seizure onset, the number and duration of each seizure episode and status epilepticus, transient attenuations and ictal discharges. An EEG seizure was described as a distinct episode of epileptiform activity observed over a minimum duration of 6 seconds and at least 9 seconds apart from another episode. Electrographic status epilepticus was defined as continuous epileptiform activity for 30 minutes. It was observed from the onset that almost all children with cerebral malaria had wave amplitudes higher than that seen in normal children. For the purposes of the study therefore, we used relative measurements and compared the wave amplitudes of the patients against each other and categorized them into three: low amplitude (<100mV), medium amplitude (100-300mV) and high amplitude (>300mV). Wave frequencies were grouped into 4: A - dominant delta activity with little or minimal theta activity (<1-2Hz), B - some delta and some theta activity (mixed frequency, 2-3 Hz), C - dominant theta activity with some delta activity and D - near normal. Each EEG recording was analyzed by two independent readers: all were analyzed by GO and some by SG and others by RI. The two reports were later checked for congruency and disparities in analysis were reviewed and discussed by the whole team. The interrater agreement between the investigators on seizure detection was excellent. Where consensus could not be reached, the recordings were sent to SW, a consultant Neurophysiologist, for clarification.

**Neurological assessment at discharge**

All surviving patients underwent a neurological examination at discharge. Standard clinical classifications were used and children with gross deficits such as motor deficits (cranial nerve palsy, spasticity and central hypotonia), ataxia, movement disorders (tremors, dystonia and choreoathetoid movements), speech (speech difficulties or
aphasia), visual (blindness) and hearing impairments, epileptic seizures, behavioral abnormalities (like new onset aggressive behavior and hyperactivity) were defined to have neurological deficits[16]. Trial participants had a similar neurological assessment 3 months after discharge from hospital. Children found to have neurological deficits are being followed up in a neurology clinic.

DATA ANALYSIS

Data was analyzed with Stata version 9 (STATA corporation, Texas). We compared the characteristics of patients with recurrences of seizures to those without. A description of the background and ictal EEG recordings was made. The EEG features of patients who died, survived with or without neurological deficits were compared describe to features associated with poor outcome. Continuous data were compared using Mann Whitney-Wilcoxon’s rank-sum test. Pearson’s chi square test (or Fischer’s exact test as appropriate) was used to compare proportions.

RESULTS

General description

Between December 2004 and March 2007, fifty-four children with cerebral malaria were recruited for continuous EEG monitoring. The recordings of two children were unsatisfactory and were excluded (equipment failure occurred in one child while the second died before an appreciable recording was made). Thirty-six of the remaining 52 children were monitored with the Nervus EEG monitor while 16 were monitored on the Grass telefactor EEG machine. The median duration of recording was 20 (IQR 12, 42) hours. Table 1 is a summary of the clinical characteristics and outcome of these patients.

The background EEG

In the majority of patients, the background EEG at admission was characterized by very slow wave activity (1-3Hz) with medium to high amplitudes (100-450μV), figure 1.

The background EEG of a 36-month old child with cerebral malaria showing generalised high amplitude slow wave activity. The vertical lines are at 1 sec intervals.

Waves with amplitudes <100μV were recorded in 7 children and dominant theta waves (4-7Hz) in only 3. No child had a normal background EEG. As the level of consciousness
Figure 1 The background EEG in a child with cerebral malaria

The background EEG of a 36-month old child with cerebral malaria showing generalised high amplitude slow wave activity. The vertical lines are at 1 sec intervals.

Table 1 Characteristics of 52 children with cerebral malaria monitored on continuous EEG

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Seizures detected on EEG monitoring</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes, n=20</td>
<td>No, n=32</td>
</tr>
<tr>
<td>Median (IQR) duration of illness, days</td>
<td>2.5 (2.3)</td>
<td>3 (2.5, 4)</td>
</tr>
<tr>
<td>Median (IQR) age, months</td>
<td>35 (27, 42)</td>
<td>32 (25, 43)</td>
</tr>
<tr>
<td>Seizures before admission, (%)</td>
<td>17 (85.0)</td>
<td>26 (81.3)</td>
</tr>
<tr>
<td>Median (IQR) number of seizures before admission</td>
<td>3 (2.7)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Mean (SD) admission temperature, °C</td>
<td>37.7 (1.2)</td>
<td>38.0 (1.2)</td>
</tr>
<tr>
<td>Features of shock (capillary refill&gt;2 sec), (%)</td>
<td>6 (30.0)</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Deep (acidotic) breathing, (%)</td>
<td>9 (45.0)</td>
<td>16 (50.0)</td>
</tr>
<tr>
<td>Depth of coma (BCS) 0</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Hypoglycaemia, (%)</td>
<td>4 (20.0)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Median (IQR) duration of EEG monitoring, hrs</td>
<td>39.0 (18.5, 60.5)</td>
<td>14.5 (10.5, 26.0)</td>
</tr>
<tr>
<td>Blood transfusion, (%)</td>
<td>2 (10.0)</td>
<td>10 (31.3)</td>
</tr>
<tr>
<td>Deaths, (%)</td>
<td>5 (25.0)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Neurological sequelae in survivors, (%)¶</td>
<td>2 (13.3)</td>
<td>5 (17.2)</td>
</tr>
</tbody>
</table>

*Chi square for trend
¶ N=44, seizures recurred=15 and did not recur=29
improved, the dominant frequency increased above the admission frequency. Concurrently, there was a decrease in the amplitude. At the end of recording when patients had regained consciousness, all surviving patients had waves with amplitudes <300μV. Children admitted with higher frequency waves had a shorter duration of coma. In these patients, the frequency at admission was ≥4Hz and the amplitude 100-200 μV. Full consciousness was regained within 8 hours of admission.

Two children were admitted with profound coma (BCS 0) and an asymmetrical background EEG characterized by lower amplitude and frequency over one hemisphere (figure 2). One died. Two other children, who both had status epilepticus, developed asymmetrical background EEG waveforms during the course of admission. After a prolonged period of hospitalization, one was discharged with quadriplegia and impaired speech. The second child initially regained full consciousness but later developed further seizures and lapsed into coma (biphasic cerebral malaria). This second period of coma lasted 38 hours and neurological deficits were not observed on discharge from hospital.

**Figure 2** Asymmetry in the background EEG in a child with cerebral malaria

Asymmetry of the background EEG of a 40-month old child with cerebral malaria on a Nervus monitor: waves over the right hemisphere have lower amplitudes in comparison with those over the left hemisphere.
Transient attenuations in the background EEG were observed in 23/52 children. This was associated with status epilepticus and multiple anticonvulsants in 8 children or with single seizures (controlled with paraldehyde or diazepam before or during the recording) in 7 other cases. Of the 23 children with transient attenuations, 5 died and 4 developed neurological deficits. One child died after developing a burst suppression pattern.

**The ictal EEG and seizures**

EEG recording started after patients had been resuscitated and stabilized. In almost all cases, this was within 2 hours of arrival to hospital. Children brought to the ward while convulsing received anticonvulsants and therefore such seizures were not captured on EEG. Only seizures after the resuscitation and stabilization period are documented.

Of the 52 children, 20 (38.5%) had seizures detected on EEG. The EEG recording time in patients who had seizures detected on EEG was two times longer than that in patients who did not have any seizures detected (table 1). A total of 372 seizure episodes were observed of which 149 (40%) were documented as electroclinical seizures. Seven children contributed most of the seizure episodes and in particular, one child who had 210 seizure episodes. Between them, the seven children had 343 seizures detected on EEG. Ictal activity was characterized by spikes and sharp waves and in a few episodes, spike and wave complexes. A generalized onset was observed in 155 (41.7%) and a focal onset in 208 (55.9%) seizure episodes. Focal seizures mostly originated over the parieto-occipital areas. Some seizures arose from the frontal, anterior and posterior temporal areas and rarely over the mid temporal region. In up to 55.3% of cases, the focal seizures especially those among the seven children with multiple seizures, involved the whole hemisphere of origin.

One child had prolonged periods of ictal activity. These were interspersed by short intervals when no ictal discharges were observed. Each seizure originated from different areas of the brain (temporal, frontal and parietal) and from either hemisphere although the left temporal area was most involved. The wave amplitude progressively decreased to extremely low values (4-30 μV) but during this period, near normal bursts of brain electrical activity and seizure discharges would appear. The child eventually died.

**Electroclinical and electrographic seizures on continuous EEG monitoring**

Of the 372 seizure episodes documented on EEG, only 149 had corresponding clinical manifestations (electroclinical seizures). The remaining 223 seizures were therefore
described as electrographic seizures. The manifestation of the electroclinical seizures (e.g. focal, generalized) corresponded with the expected EEG manifestations in only 39% of episodes: 34% of the seizures detected clinically as focal seizures appeared generalized on EEG and 75% of seizures with subtle manifestations were generalized on EEG. Subtle seizures made up 30% of all electoclinical seizures. These were often described as blank stares, twitching of oro-facial muscles and limb digits, nystagmoid eye movements, irregular respiration and frothing. Most electrographic seizures (139/223 [62.3%]) were focal seizures that originated over the frontal lobe, anterior and posterior temporal regions or the parietal and occipital lobes. Table 3 shows the types of clinical seizures compared with the corresponding seizure detected on EEG and the types of electrographic seizures.

Two thirds of both electroclinical and electrographic seizures lasted <5 minutes (table 4). On average, electroclinical seizures lasted one minute longer than electrographic seizures: the median duration of electrographic seizures was 3.2 (IQR 1.2, 8.0) minutes while that of electroclinical seizures was 4.3 (IQR 2.1, 9.9) minutes, \( p=0.004 \).

Status epilepticus was observed in 11 patients. Electrographic status epilepticus was observed in 6 children and was associated with poor outcome: three children died and the fourth was discharged with multiple neurological deficits. In all cases, electrographic status was observed in children who had electroclinical status epilepticus before or after admission to hospital and had been controlled with anticonvulsants.
Abnormal EEG patterns and specific clinical events

EEG during abnormal motor posturing

Among patients with abnormal motor posturing, the background EEG was characterized by very high amplitude (300-500 μV) and low frequency (1-3 Hz) waves. During periods of decorticate posturing, the background EEG changed to a very slow (<1-2 Hz) generalized high amplitude (450-600 μV) waves. In one child, the waves reached a peak of 775 μV. These changes were observed intermittently and each episode lasted 1-4 minutes. There were no epileptic discharges during any of these events. Similar changes in amplitude and frequency were observed in children with decerebrate posturing. However, in one child with decerebrate posturing, epileptic spike and sharp wave discharges were observed in addition.

Rhythmic runs

We observed rhythmic runs in 3 children. These occurred both, in association with or without seizure discharges. One child, a 33-month old boy, had multiple and prolonged runs of such rhythmic activity over both hemispheres and not associated with any epileptiform discharges. This continued for several hours although there were short intervening periods of slow wave activity. On discharge from hospital, the child had a normal neurological examination. Another child, an 18-month old girl, was admitted with electrical status epilepticus refractory to multiple anticonvulsants. During the short interictal periods, she exhibited bilateral runs of rhythmic activity most marked over F3. She had decerebrate posturing associated with sharp waves and spikes during the periods of posturing and eventually died.

Non-seizure events

Four children had short-lived clinical seizure-like events not accompanied by any epileptiform activity on the EEG. There were 10 such events in the four patients. Eight were described as "focal seizures" (manifested as clonic movements of the upper limb), one as a "generalized seizure" and another as a "subtle seizure". Three of the four children had other seizure events at different times. All survived without deficits.

Outcome of cerebral malaria

Eight children (15.3%) died and of the 44 surviving children, 7 (15.9%) had neurological deficits on discharge from hospital. The characteristics of the 15 patients with poor outcomes are presented in tables 4 and 5.
Six out of eight deaths occurred within 48 hours of admission and in four patients, this was associated with status epilepticus. Respiratory arrests followed status epilepticus and multiple anticonvulsants. Among survivors, patients without additional seizures regained consciousness faster (median [IQR] duration 25 [10, 50] hours) than those with further seizures, (44 [22, 72] hours). Neurological deficits on discharge included hemiparesis, paraparesis, quadripareisis, ataxia, speech and visual impairments. Children who developed deficits also had a longer duration of coma, table 5. Neurological deficits were associated with status epilepticus (before or after admission to hospital) and features of raised ICP. Three other children had behavioral abnormalities (aggressive behavior and hyperactivity) documented 3 months after discharge.
DISCUSSION

We carried out prospective observations with continuous EEG in 52 children who fulfilled the WHO definition of cerebral malaria. Seizures were detected in 40% of patients after the initial period of resuscitation on admission. Majority of recurrent seizures were electrographic and occurred in a few individuals initially admitted with status epilepticus. There was little congruence between the electroclinical seizure manifestations and the EEG characteristics. Very slow or asymmetrical EEG background on or during the course of admission and electrographic status epilepticus were associated with poor outcome.

The characteristics of the background EEG in cerebral malaria and prognosis

The background EEG in children with cerebral malaria is characterized by non-specific features – generalized slowing and high amplitude waves. The degree of slowing reflects the severity of the encephalopathy. Recovery is associated with an increase in the
background frequency and a reduction in the amplitude. However, large decreases in amplitude are pre-terminal events. Specific features in the background EEG and in particular, asymmetry between the two hemispheres is associated with poor prognosis. The pathological changes resulting in asymmetrical waves are unclear. However, out of four children with asymmetry, one died, the second was discharged with quadriparesis and impaired speech and the third, developed biphasic cerebral malaria (relapsed into coma after an initial period of recovery of consciousness). Asymmetry of the background EEG was associated with profound coma and status epilepticus, both poor prognostic features in children with cerebral malaria[6]. Local events (e.g. ischemia) over the affected hemisphere may be important pathogenic factors. Imaging studies such as magnetic resonance imaging (which was unavailable to us) may be useful in establishing the underlying pathology. On the other hand, children with less severe encephalopathy had background EEG with wave frequencies ≥4Hz, a good outcome and rapidly regained

### Table 5 Characteristics of children who survived with neurological sequelae

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, months</td>
<td>38</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Duration of illness, days</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Duration of coma before admission, hours</td>
<td>8</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Parasite density, /ml</td>
<td>372.78</td>
<td>402.8</td>
<td>706.68</td>
</tr>
<tr>
<td>Status epilepticus before admission</td>
<td>Yes</td>
<td>No</td>
<td>Yes, controlled with diazepam and paraldehyde</td>
</tr>
<tr>
<td>Status epilepticus after admission</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Number of seizures after admission</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total duration of seizures after admission to hospital, minutes</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| Background EEG on admission | Slow 2-3Hz medium amplitude waves slows with each episode of posturing, background symmetrical | Very slow (1-2Hz) medium amplitude, symmetrical background, several episodes of transient attenuations | Very slow (1-2Hz) medium amplitude waves symmetrical background |
| Ictal discharges and localization of ictal activity | Anterior frontal | No further epileptic discharges after initial status epilepticus | No further epileptic discharges after initial status epilepticus |
| Types of clinical seizures in ward | Secondarily generalised | - | - |
| Electrographic seizures | No | No | No |
| Other significant events | Decorticate posturing Opisthotonic posturing | |
| Time to full consciousness, hours | 40 | 61 | 64 |
| Neurological sequelae at discharge | Impaired speech | Hemiparesis | Impaired vision |
consciousness suggesting that, an EEG during the acute phase might be a useful tool in predicting the outcome of children with cerebral malaria.

Transient periods of attenuations in the background EEG were associated multiple anticonvulsant drugs for recurrent seizures. The association between transient attenuations, multiple doses of CNS depressant anticonvulsants (e.g. diazepam) and death suggest that apart from the seizures, some deaths might have been due to the CNS depressant effects of multiple doses of anticonvulsant drugs. A burst suppression pattern was a pre-terminal event.
Seizures on continuous EEG monitoring

The majority of recurrent seizures (both electroclinical and electrographic) were detected in a few children. The patients were initially admitted with status epilepticus that appeared to respond to anticonvulsants. In the ward, they continued to have prolonged periods of epileptic discharges. The previous study of serial EEGs in children with cerebral malaria using a 12-lead EEG machine suggested that the majority of recurrent seizures were focal seizures that originated over the posterior temporal and parietal regions, a watershed area that lies in the cortex supplied by distal branches of the middle cerebral and posterior cerebral arteries and concluded that ischemia and hypoxia may be important in the causation of these seizures[8]. Compared to the previous study, the current study has two additional strengths: continuous rather than serial monitoring and more (16 and 21) EEG leads and therefore improved seizure detection and localization. Most seizures had a focal origin but among the seven patients with multiple seizures, discharges originating over a whole hemispheric were common. Focal seizures were observed to arise over the frontal lobes, and the anterior and posterior temporal regions. In addition, about one third were from the parieto-occipital area, a region served by the posterior cerebral artery whose flow is most at risk of compromise by raised ICP. Transcranial Doppler studies of blood flow in these vessels may be useful.

This study clearly demonstrates that clinical observation alone only detects a smaller proportion of seizures in children with cerebral malaria and in particular in children with status epilepticus. Without EEG monitoring, the frequency of seizures is grossly underestimated. Electrographic seizures formed 60% of the total number of seizures in this cohort and electrographic status was associated with poor outcome. Similar findings have been described in other settings in patients with convulsive status epilepticus on continuous EEG monitoring after the convulsive seizures had been ablated with anticonvulsant therapy[12]. Although the majority were observed in patients who had status epilepticus, in comatose patients, these electrographic or non-convulsive seizures can also develop after single seizures[10]. The study suggests that unrecognized electrographic status epilepticus might be a major cause of death and neurological deficits in children with cerebral malaria. Similar poor outcomes have been described in neonates with electrographic seizures in studies which suggested that electrographic seizures may have neuron damaging effects similar to electroclinical seizures[17, 18]. Physiological studies suggest that damage may arise from the failure to increase arterial blood pressure and flow to match cerebral metabolic needs[19].

Non-seizure events such as abnormal motor posturing (decorticate, decerebrate and opisthotonus posturing), rigidity, tremors and chewing movements with sudden changes in pulse, oxygen saturation or blood pressure were observed in some children. Although such events are not seizures, in the absence of EEG evidence, the clinical staff
may document them as seizures. Anticonvulsant drugs with their attendant risks of respiratory depression might be administered to these children. Using the EEG, we were able to exclude 10 such episodes initially documented as seizures by the nursing team. We however acknowledge that at present, continuous EEG monitoring may be out of reach of most district hospitals in sub-Saharan Africa where the majority of children with cerebral malaria are treated. The costs involved and absence of personnel are major prohibitive factors.

Only seizures occurring after the initiation of the EEG recording were documented. In addition, the study was performed in the context of a trial of fosphenytoin for the prevention of recurrence of seizures. Pharmacokinetic studies suggest that fosphenytoin prevents over 50% of recurrent seizures in children with severe malaria[20]. The first 38 study subjects were part of this trial and had been randomized to receive either fosphenytoin or placebo. Put together, these factors could have led to an underestimate of the overall burden of seizures in these patients.

The WHO definition for cerebral malaria is not specific[21]. Recent studies suggest that cerebral malaria in African children is characterized by distinct changes in the retina (macular and peripheral retinal whitening, white and orange vessel changes, white centred retinal hemorrhages and different grades of papilloedema) on indirect ophthalmoscopy [22-24]. Future studies of the EEG in cerebral malaria should include detection of these signs in the definition of the disease.

CONCLUSION

In conclusion, children with cerebral malaria and in particular those admitted with convulsive status epilepticus experience a big burden of electrographic seizures and electrographic status epilepticus is associated with poor outcome. Continuous EEG monitoring is a useful tool for the detection of such seizures and the acute EEG may be of prognostic value.

REFERENCES


