A retrospective observational study of EEG findings and antiepileptic drug use among children referred for EEG to Zambia’s University Teaching Hospital

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SUMMARY

Objective: Despite the heavy burden of epilepsy in Sub-Saharan Africa, there remains a relative paucity of neurophysiology services and limited published data on electroencephalography (EEG) features among African children. The aim of this study was to describe clinical characteristics, EEG findings, and antiepileptic drug (AED) use among children referred for EEG to the University Teaching Hospital in Zambia.

Methods: EEG referrals and reports from 2013–2015 were reviewed. Within the context of routine care, EEG studies were interpreted by readers with advanced training in child neurology and clinical neurophysiology. Clinical data provided in the referral including seizure semiology and EEG findings were systematically extracted and analyzed.

Results: A total of 1,217 EEG reports were reviewed, with 1,187 included in the analysis. Median age was 7 years (interquartile range [IQR] 3–11) and 57% were male. Seventy-three percent of 554 had documented seizure onset before 5 years of age. Among the 23% with seizure etiology documented, 78% were associated with perinatal injuries and central nervous system (CNS) infections. EEG abnormalities were found in 75% of the studies. Clinical semiology per referral identified focal seizures in 29%, but EEG findings increased this proportion to 63% (p = 0.004). Sixty-two percent were taking AEDs, with 85% on monotherapy. The most commonly used AED was carbamazepine (49%). There was no association between the choice of AED and clinical semiology (all p’s > 0.05).

Significance: This tertiary care center study identified >60% of referred children to have localization-related epilepsies, with at least 18% of epilepsies being from potentially preventable causes. These findings are consistent with multi-country, population-based data from elsewhere in Africa. Seizure semiology assessed in routine, nonspecialist care does not predict AED choice, and the presence of focality is underestimated in routine care.

KEY WORDS: Epilepsy, Electroencephalography, Antiepileptic drugs, Children, Africa.
This study adds to the limited data on EEG findings in African children with epilepsy. At least 18% of children referred had a history of perinatal injuries and CNS infections as a probable cause for their epilepsy, suggesting that preventable causes contribute significantly to the burden of epilepsy in Africa. Localization-related epilepsy was clinically suspected in only 29% of children, but EEG studies were suggestive of focal seizures in 63%. The most commonly used AED was carbamazepine. Seizure semiology did not predict AED selection at EEG referral. EEG services may optimize epilepsy care for children with refractory seizures.

2011 rural population-based survey previously identified age-specific prevalence rates to be highest among children 5–15 years old (26.2/1000). Although electroencephalography (EEG) technology is not necessary to make a diagnosis of epilepsy and initiate treatment, EEG plays a unique role in diagnosing specific epileptic syndromes, such as West syndrome, that are of particular relevance in pediatric populations and may require specific interventions. In SSA there is a relative paucity of pediatric neurophysiology services, with few published reports of the EEG findings in African children with epilepsy. Where EEG data have been ascertained, findings have informed individual clinical care and provided potential insights relevant to health services priorities and public health.

A 2014 systematic review identified published reports detailing EEG findings among general populations of people with epilepsy from 7 SSA countries. The EEG findings varied widely even within the same country, possibly due to the use of different classification systems and the studied regions being selected for special exposures or conditions. It is notable that there is no validated screening instrument for the identification of nonconvulsive seizures, so EEG data from cases identified in population-based studies are significantly biased toward inclusion of people with epilepsy who experience at least some generalized seizures. Given this challenge, pragmatically, EEG data from clinic-based samples may provide more accurate profiles of seizure subtypes than data semiology from community-based cohorts. A recent study conducted in 5 African countries (South Africa, Tanzania, Uganda, Kenya, and Ghana) to determine the prevalence and pattern of EEG abnormalities in people affected by active convulsive epilepsy (ACE) using a single routine EEG included 679 children. EEG abnormalities were present in 59%, with 52% among all ages having focal features. EEG abnormalities at individual study sites were associated with adverse perinatal events, neurocognitive impairment, AED use, and seizure frequency, but none of these factors were significant at all study sites, highlighting the importance of site-specific data and interventions.

The aim of the present study was to describe EEG findings as well as the clinical characteristics including AED use and seizure semiology per the referral, in children aged 1 month to 18 years referred for EEG examination to the University Teaching Hospital in Lusaka, Zambia over a 3-year period.

### Methods

A retrospective observational study of EEG records of children seen at the University Teaching Hospitals (UTHs) in Lusaka (population 2 million) from January 1, 2013 to December 30, 2015 was performed. Zambia has a population of 16 million, with half of the population under the age of 15 years. The UTH is the national referral hospital in Zambia, which provides care for an average of 25,000 to 30,000 children annually. Care at UTH is free but travel and indirect costs related to caregiver upkeep are barriers to care seeking.

At the time of the study, UTH had the only pediatric EEG service in the country, with EEG provided free of charge. Children requiring EEG were referred by pediatricians or other clinicians practicing in government or private health institutions. A digital video-EEG (EBI NEURAL) with 24 monopolar and 4 bipolar channels was performed using the 10–20 system with polygraphy recording. Routine awake EEG recordings were 20–30 minutes in duration and included hyperventilation and intermittent photic stimulation. When a sleep EEG was requested, children were sedated using melatonin according to age (1.5 to 4.5 mg) and EEG duration was 45–60 minutes. Over the course of the study, structured EEG reports for clinical care were generated independently by one of the 5 readers according to routine clinical practice. All the readers had advanced training in child neurology and/or clinical neurophysiology.

All EEG referrals and reports for children aged 1 month to 18 years were reviewed. Data were extracted and transferred to a structured data collection tool; information on patient demographics, clinical information including AED use at referral, seizure semiology per referral, and EEG characteristics were extracted, with particular attention to EEG findings that could direct AED selection. Anonymized data were captured in an electronic database using EPI-DATA. An EEG was considered “positive” if there were any abnormalities including abnormalities of the background activity, interictal epileptiform activity, ictal discharges, or abnormal responses for age to activation procedures.

Data were analyzed using STATA version 12.1 (StataCorp, College Station, TX, U.S.A.). The main outcome...
variables were EEG abnormalities. Descriptive statistics were used to summarize patient characteristics and the EEG abnormalities observed using means, medians, or percentages as indicated. Logistic regression was performed to determine the associations between patient characteristics, clinical characteristics, types of seizure, and the EEG findings. Descriptive data indicated where data were missing and analyses were limited to those cases with data available.

The study was approved by the University of Zambia, Biomedical Research Ethics Committee.

**RESULTS**

A total of 1,217 EEG reports were reviewed; 30 (2%) were excluded due to an incomplete report or duplication of records. Of the 1,187 children included in the analysis, the median age at EEG request was 7 years (IQR 3–11) and 57% (672) were male. Seventy-three percent (403) of 554 children had documented seizure onset before the age of 5 years. Epilepsy etiology was provided in 23% (278) of referral documents and among these 78% (217) were attributed to perinatal injuries and CNS infections (Table 1). Only 17% (207) of the children had their HIV status documented on the EEG request, and of these 24% (50) were HIV seropositive.

The clinical indications for EEG were epileptic seizures (88%, 1,044), status epilepticus or nonconvulsive status epilepticus (3%, 39), febrile seizures (3%, 37), and probable nonepileptic events (6%, 67) such as syncope, migraine, or bruxism. Among the 1,044 (88%) referred for epileptic events, the seizures were clinically described in 77% (805), with 64% (517) being generalized, 29% (230) focal, and 7% (58) multiple seizures types. In the remaining 23% (239), no description of the epileptic events was provided on the EEG requisition other than “fits,” “convulsions,” or “seizures.”

A sleep EEG was obtained in 71% (843) of the studies. Melatonin was used for sedation prior to EEG in 35% (417) and successfully induced sleep 77% (321) of the time (Table 2). This is consistent with recent reports of melatonin use for EEG sedation.15 Photic stimulation was performed in 29% (342) of EEG studies, and only 1% (4) of these demonstrated a photoparoxysmal response.

EEG abnormalities were found in 75% (889) of the studies. Abnormal background activity was present in 41% (490) of all the EEG recordings reviewed. Intercital epileptiform activity was observed in 70% (839); of these, focal activity with a single foci was the most common finding seen in 63% (526), followed by multifocal in 28% (235) and generalized in 9% (78) (Fig. 1). Ictal events during EEG were recorded in 11% (127) of patients, of which 39% (50) were consistent with focal-onset seizures. Male gender (p = 0.001), age below 5 years (p < 0.001), and having an epileptic seizure as a clinical indication for EEG (p < 0.001) were all significantly associated with EEG abnormalities.

Based on clinical semiology, only 29% (230) of children were reported to have focal onset seizures, but EEG findings

| Table 1. Participants clinical information and EEG abnormalities |
|---------------------------------------------------------------|
| **Patient characteristics** | **Normal EEG** | **Abnormal EEG** | **Total** | **p-Value** |
| Gender (n = 1,187) | | | | |
| Male | 145 (22) | 527 (78) | 672 (57) | 0.001 |
| Female | 153 (30) | 362 (70) | 515 (43) | |
| Clinical indication for EEG (n = 1,187) | | | | |
| Epileptic seizure | 219 (21) | 825 (79) | 1,044 (88) | <0.001 |
| SE/NCSE | 7 (18) | 32 (82) | 39 (3) | |
| Febrile seizures | 15 (41) | 22 (59) | 37 (3) | |
| Nonepileptic events | 54 (81) | 13 (19) | 67 (6) | |
| Age at onset of seizures (n = 554) | | | | |
| 0–11 months | 22 (14) | 132 (86) | 154 (28) | <0.001 |
| 1–5 years | 54 (22) | 195 (78) | 249 (45) | |
| 6–11 years | 34 (32) | 73 (68) | 107 (19) | |
| 12 and older | 21 (48) | 23 (52) | 44 (8) | |
| Clinical description of seizures (n = 805) | | | | |
| Generalized | 116 (22) | 401 (78) | 517 (64) | 0.306 |
| Focal | 48 (21) | 182 (79) | 230 (29) | |
| Multiple seizure types | 8 (14) | 50 (86) | 58 (7) | |
| Etiology (n = 278, 23%) | | | | |
| Perinatal event | 12 (10) | 104 (90) | 116 (42) | 0.170 |
| CNS infection | 19 (19) | 82 (81) | 101 (36) | |
| Other | 11 (18) | 50 (82) | 61 (22) | |
| HIV status (n = 207) | | | | |
| Positive | 8 (16) | 42 (84) | 50 (24) | 0.691 |
| Negative | 29 (18) | 128 (82) | 157 (76) | |

*Perinatal event: 47% of perinatal events were due to hypoxic-ischemic encephalopathy.

*SE/NCSE, status epilepticus/nonconvulsive status epilepticus.
increased this proportion to 63% (526) (p = 0.004). The report of clinical focality was predictive of EEG focality (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.1–2.6). Children older than 5 years were more likely to have focal epileptiform activity detected on EEG (OR 1.8, 95% CI 1.1–2.6). A report of clinical focality was predictive of EEG focality compared to 40% (68) with generalized and multifocal discharges (p < 0.001). Sodium valproate was used in 16% (47) of the patients with EEG focality versus 25% (42) with generalized and/or multifocal discharges (p = 0.002). Phenobarbitone was used in 26% (76) of the patients with focality versus 35% (61) with generalized and/or multifocal discharges (p = 0.003). Based on the EEG findings alone, patients with EEG focality were twice as likely to be receiving carbamazepine compared to valproate or phenobarbitone (OR 2.0, 95% CI 1.4–3.0) (Table 4).

Carbamazepine was used in 57% (166) of patients with EEG focal epileptiform activity compared to 40% (68) with generalized and multifocal discharges (p < 0.001). Sodium valproate was used in 16% (47) of the patients with EEG focality versus 25% (42) with generalized and/or multifocal discharges (p = 0.002). Phenobarbitone was used in 26% (76) of the patients with focality versus 35% (61) with generalized and/or multifocal discharges (p = 0.003). Based on the EEG findings alone, patients with EEG focality were twice as likely to be receiving carbamazepine compared to valproate or phenobarbitone (OR 2.0, 95% CI 1.4–3.0) (Table 4).

Thirty-seven percent, or 7 of the 19 patients with electroclinical features consistent with IGE were not receiving treatment at the time of the recording (4 with CAE, 1 with JME, 1 with EMA, 1 with GTCS). The remaining patients with diagnosis of IGE were 37% (7) on carbamazepine and 26% (5) on sodium valproate.
Despite the prevalence of epilepsy in the pediatric population of SSA, limited data have been published about the main EEG features of children in this region of the world. This retrospective observational study from an academic medical center in Zambia is limited due to the inevitable nature of referred patients (i.e., referral bias) rather than a representative sample from the population. This might have resulted in more severe epilepsies being included here. Alternatively, proximity to the referral center and family economic means may have impacted who was included in this study. Nonetheless, this study highlights that at least among the children referred and presenting to an academic medical center for an EEG, the majority had seizure onset before the age of 5 years. This is in keeping with observations made in SSA as well as in other regions of the world.5,16 This early onset is likely secondary to epilepsy caused by perinatal events resulting from hypoxic-ischemic encephalopathy and early CNS infections, as was the case with at least 18% of children in this Zambian study. If a

**Table 3. Antiepileptic drug use in children referred for EEG**

| AEDs (n = 735, 62%) | Frequency | Percentage (%) |
|---------------------|-----------|----------------|
| Monotherapy         | 622       | 85             |
| Polytherapy         | 113       | 15             |
| AEDs used for monotherapy (n = 622) |          |                |
| Carbamazepine (CBZ) | 304       | 49             |
| Phenobarbitone (PB) | 188       | 30             |
| Sodium valproate (VPA) | 127     | 20             |
| Others              | 3         | <1             |
| AEDs used for polytherapy (n = 113) |          |                |
| VPA + PB            | 26        | 23             |
| PB + CBZ            | 24        | 21             |
| VPA + CBZ           | 16        | 14             |
| VPA + CLZ           | 11        | 10             |
| VPA + LTG           | 6         | 5              |
| VPA + CBZ + PB      | 6         | 5              |
| VPA + LEV           | 3         | 3              |
| Others              | 21        | 19             |

LTG, lamotrigine; CLZ, clonazepam; LEV, levetiracetam.

1 Combination of either CBZ/VPA/PB with LTG/LEV/CLZ/DZP/prednisolone.

**Figure 1.**
Flow chart of EEG findings.

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significant proportion of childhood epilepsy in this region is due to potentially preventable causes, then the high prevalence of epilepsy could be addressed through improved perinatal care, expanded vaccination programs, and/or improved infection control. Prior research in Zambia evaluating people with HIV and new-onset seizure has shown a high prevalence of EEG abnormalities as well as high mortality rates in adults with advanced HIV infection. Unfortunately, we were unable to evaluate the effects of HIV infection on EEG findings in this high HIV prevalence setting due to limited HIV data in the EEG referral record.

A large proportion of EEG recordings in this study were abnormal, with the majority of abnormalities being focal epileptiform activity. The high prevalence of focal abnormalities found in this study is consistent with the result of other studies conducted in the SSA suggesting identifiable and preventable causes of epilepsy. In our study we found substantial discordance between clinical seizure semiology noted by referring clinicians who described the majority of seizures as generalized (64%), compared to the predominance of focal abnormalities (63%) found on EEG studies. A similar discrepancy between diagnoses based on clinical history alone versus diagnoses supported by electrographic findings has been found in other studies conducted in the region. A study conducted in West Uganda (in an area of high epilepsy prevalence, known to be endemic for onchocerciasis), revealed that when seizures were described based on seizure description alone, the predominant seizure was classified as generalized (63%), but when EEG results were also used to classify seizure type, the proportion of generalized seizures fell to 22%. More recent studies conducted in tertiary referral centers in Nigeria comparing clinical and EEG diagnoses, revealed a significant discrepancy between diagnoses made on clinical features alone versus EEG diagnosis. Although a single routine awake and sleep EEG has admittedly limited sensitivity and specificity, and a single observation of focal EEG abnormalities cannot confidently discount the possibility of a generalized seizure, the discrepancy noted in our study and in similar studies in our region in which clinicians overestimate generalized epilepsies while failing to identify localization-related seizures, is likely driven by insufficient time and expertise for the referring health provider to distinguish seizure semiology and ascertain fociability. An important consideration is that in settings such as Zambia where most epilepsy care is provided by overburdened and undertrained non-physician healthcare providers, EEG availability may be more accessible than neuroimaging. Consequently, where neuroinfections are a common cause for focal seizures and access to neuroimaging is limited and costly, potentially treatable conditions such as neurocytecteriosis may be otherwise missed. Finding EEG focality in such cases can prompt the need for neuroimaging and/or assist in leveraging access to imaging. Correct identification of focal-onset seizures as well as other seizure types is also very important for cost-effective use of the available AEDs.

The low prevalence (1%) of photoparoxysmal responses on EEG when intermittent light stimulation was performed, seems to confirm the findings of 2 large studies conducted in Zimbabwe, which revealed that EEG photoparoxysmal responses (PPRs) have a lower incidence in black African populations compared to the Caucasian and Asian populations. Genetic rather than environmental factors were considered the primary cause of the difference in prevalence of PPRs to photic stimulation. Of course, referral bias may also play a role in these differences.

Our findings also determined that the majority of the patients on AEDs were on monotherapy, with only 12% of the patients on dual therapy and less than 3% on 3 or more AEDs. These data show a positive trend in management of pediatric epilepsy at a tertiary care level compared to local primary health facilities where use of multiple combination and incorrect dosing of AEDs is not uncommon. The use of polytherapy in our study was less frequent than what has been reported from a tertiary care hospital in New Delhi, India, where polytherapy with 2 and greater than or equal to 3 AEDs were prescribed in 34.9% and 27.2% of the patients, respectively.

The analysis of the use of AEDs in relation to clinical descriptions of seizures showed that there was no association between the choice of AEDs and clinical seizure semiology (focal vs. generalized or mixed type of seizures). These results suggest that seizure semiology assessed in routine, nonspecialist care does not appear to influence AED choice. AED may be mainly determined by drug availability and established medical practices. Carbamazepine was the most commonly prescribed AED; it is widely

| Drug | Gen/poly | Focal | Total | OR (CI) | p-Value | No | Yes | Total | OR (CI) | p-Value |
|------|----------|-------|-------|--------|---------|-----|-----|-------|--------|---------|
| CBZ  | 167 (70) | 71 (30) | 238 (100) | 1.3 (0.9-2.0) | 0.182 | 68 (29) | 166 (71) | 234 (100) | 2.0 (1.4-3.0) | <0.001 |
| VPA  | 74 (77)  | 22 (23) | 96 (100)   | 0.7 (0.4-1.3) | 0.297 | 42 (47) | 47 (53)   | 89 (100)   | 0.6 (0.4-1.0) | 0.029  |
| PB   | 100 (75) | 34 (25) | 134 (100)  | 0.9 (0.6-1.4) | 0.587 | 61 (45) | 76 (55)   | 137 (100)  | 0.6 (0.4-0.9) | 0.034  |

Subtotal | 343 | 128 |

*Includes 1% of other drugs not included in the chart.
available and less expensive than sodium valproate. As drug of choice for focal-onset epilepsy, carbamazepine remains a cost-effective treatment in countries with high prevalence of localization-related epilepsies, although given prescribers’ limited ability to rule out primary generalized seizures, the use of carbamazepine could potentially worsen seizures in many. Sodium valproate was used more frequently in patients with generalized and/or multifocal discharges. Sodium valproate is a wide-spectrum AED effective in both generalized and focal seizures, but due to the higher cost and limited availability in low-resource settings, its use should be prioritized in the treatment of primary generalized epilepsies and HIV-related seizures.

Furthermore, sodium valproate should be used with caution in children younger than 2 years of age and avoided in suspected metabolic disorders and in women of childbearing age due to its potential teratogenic effects. Phenobarbital was used in about one-third of the patients referred for EEG. Historically, phenobarbital has been the mainstay of epilepsy management in SSA, having the advantages of broad spectrum coverage (although with poor efficacy in absence and myoclonic epilepsy) and a simple dosing regimen at a very low cost. In the past decade, the introduction and expansion of drug regulatory activities and enforcement have significantly increased the cost of phenobarbital and diminished the overall availability, leading to significant negative effects on the treatment of epilepsy, particularly in remote areas where phenobarbital is the only accessible AED. The disappearance of phenobarbital further escalates the need for electrodiagnostic insights at the individual and population level in SSA. In the absence of phenobarbital, epilepsy treatment options in low- and middle-income SSA settings consist of first-generation antiepileptic medications that come at a greater cost and/or offer benefit for a narrower range of seizure types. Unfortunately, only a minority of people with epilepsy in SSA will ever undergo an EEG for further classification of their condition, and most healthcare workers providing services for epilepsy patients do not have the clinical expertise to discriminate seizure subtypes at the level required to make reasonable decisions regarding medication selection. The use of phenobarbital in children has also been source of concern due to its unfavorable profile on cognitive and behavioral functions. However, studies conducted in adult populations in China and in children in India, have demonstrated no significant differences in cognitive and behavioral test scores, between treatment and control participants, if not some improvements as a result of a better seizure control. A careful evaluation of “risk and benefit” between the potential negative effect of phenobarbital on the developing brain and the neurologic damage due to uncontrolled seizures and status epilepticus is certainly warranted.

Notable in this study is the limited number of EEG findings consistent with idiopathic generalized epilepsies, representing only 2% of the studies. These findings probably reflect the fact that the majority of the epilepsies in our setting are symptomatic; they may also represent referral bias for more devastating epilepsies and the limited ability of primary healthcare providers to recognize more subtle seizures that are not clinically convulsive. Only 5 patients (26%) with IGE were on the most appropriate available treatment (VPA) at the time of the recording, whereas the others were either on carbamazepine, potentially worsening the seizures, or without treatment at all. These findings highlight the need for further training of health practitioners in the diagnosis of IGE and the correct choice of first-line AEDs.

A notable limitation of this retrospective study was the amount of clinical data available for each EEG reviewed. Despite the use of a standardized order form for EEG studies, there was insufficient clinical information on perinatal history, pre-existing neurologic disease, HIV status, and other comorbidities. Medical personnel in primary healthcare facilities may not have the necessary time and training for a comprehensive clinical history and ascertainment of seizure semiology. This may represent a challenge in the correct use of EEG results, as very few clinicians are familiar with EEG terminology and electroclinical correlation in our setting. Another limitation is that this work detailed only a single initial EEG in most patients. Repeated EEG studies were obtained in <2%, and these were mainly among admitted patients.

This is the first EEG study done in Zambia, and one of the few in SSA, using standard EEG requirements and clinical expertise to describe the main electroencephalographic features of children. The majority of the EEG studies were conducted in both wake and sleep increasing the detection of epileptiform activity which could have been missed by the use of standard awake EEG. It also highlights the use of AEDs in relation to EEG findings and clinical description of seizures.

**Conclusion**

This study suggests a high prevalence of potentially preventable, localization-related epilepsies consistent with multicountry, population-based data from elsewhere in Africa. Seizure semiology assessed in routine, nonspecialist care does not appear to influence AED choice, and it frequently fails to identify focality evident on EEG. Although EEG is not required to make a diagnosis of epilepsy and to initiate treatment, its importance in accurate identification and appropriate treatment of less-obvious forms of epilepsy and specific childhood electroclinical epileptic syndromes cannot be underestimated.

A more in-depth training of medical personnel at primary and tertiary health facilities on clinical diagnosis of epilepsy, seizure semiology, use of investigations, and appropriate choice of AEDs, as well as efforts to ensure availability of the appropriate range of AEDs needed for treatment, would lead to more timely and appropriate
management of epilepsy in a majority of patients. This is of particular importance in low-resource settings with paucity of neurophysiology services and limited availability of AEDs.

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DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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