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ORIGINAL RESEARCH

Poor Seizure Control Among Children Attending a Tertiary Hospital in South Western Uganda – A Retrospective Study

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Background: Seizure control among children with epilepsy (CWE) receiving anti-seizure medications (ASMs) remains a challenge in low-resource settings. Uncontrolled seizures are significantly associated with increased morbidity and mortality among CWE. This negatively impacts their quality of life and increases stigma.

Aim: This study determined seizure control status and described the factors associated among CWE receiving ASMs at Mbarara Regional Referral Hospital (MRRH).

Methods: In a retrospective chart review study, socio-demographic and clinical data were obtained from 112 medical records. CWE receiving ASMs for at least six months and regularly attending the clinic were included in the study. Physical or telephone interviews were conducted with the immediate caregivers of the CWE to establish the current seizure control status of the participants.

Results: A total of 112 participants were enrolled. Of these, three-quarters had generalized onset seizures, 23% had focal onset seizures, while 2% had unknown onset motor seizures. About 60.4% of the study participants had poor seizure control. Having a comorbidity (*p*-value 0.048, AOR 3.2 (95% CI 1.0–9.9)), history suggestive of birth asphyxia (*p*-value 0.014, AOR 17.8 (95% CI 1.8–176.8)), and being an adolescent (*p*-value 0.006, AOR 6.8 (95% CI 1.8–26.6)) were significantly associated with poor seizure control.

Conclusion: Seizure control among CWE receiving ASMs at MRRH remains poor. Efforts geared to addressing seizure control and optimizing drugs are needed, especially among children with comorbidities, those with history of birth asphyxia, and adolescents.

Keywords: epilepsy, anti-seizure medications, children, seizure control, Uganda

Introduction

Epilepsy is a common neurological disorder affecting over 50 million people of all ages.[1] Up to 80% of the estimated people with epilepsy live in low- and middle-income countries.[2] Worse still, a higher prevalence is reported among children in rural areas of undeveloped countries at 3.6–44/1000 compared to 3.5–5.5/1000 in developed countries.[3] In Uganda, the general prevalence of epilepsy is 10.3/1000 population with the highest peak among children aged 0–5 years at 30.2/1000 population.[4]

Nearly 70% of people with epilepsy become seizure-free with anti-seizure medications (ASMs).[5] Non-adherence to ASMs leads to increased seizure frequency and sudden death in epilepsy.

Seizure control not only improves the quality of life but also reduces the associated epilepsy stigma and is an important outcome measure of epilepsy control.[6] Seizure control status at six months of treatment can reliably predict long-term seizure control and allow for early interventions and referral where need be.[7] One study in central Uganda reported that nearly half of the children with epilepsy had poor seizure control.[8] Various factors have been reported to cause poor seizure control among CWE,

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including the age of seizure onset, type of seizure, non-compliance to ASMs, sleep deprivation, watching television for long hours, and multiple ASMs.[8–10] Information regarding seizure control is lacking in other regions of Uganda, therefore we set out to determine seizure control and describe the associated clinical factors among CWE at Mbarara hospital.

Materials and Methods

Study Design

This was a retrospective chart review based on the primary data collected through patient records from the pediatric epilepsy clinic at Mbarara Regional Referral Hospital (MRRH) in Mbarara, Uganda. A total of one hundred and twelve (112) chart reviews of CWE receiving ASMs were carried out during the study period.

Setting

The study was conducted at the pediatric epilepsy clinic at Mbarara Regional Referral Hospital (MRRH). MRRH is a public regional referral hospital located in south western Uganda, in Mbarara city about 260 km from Kampala, the capital city of Uganda, with a bed capacity of 350. The pediatric epilepsy clinic is an epilepsy-specialized outpatient clinic for CWE and runs on every Wednesday from 0800 hrs to 1600 hrs. The clinic is run by a pediatric neurologist, a medical officer, master of medicine (pediatrics), child health students, electro-encephalogram technician, and nurses. The clinic keeps both hard copy and soft copy medical records.

Participants

The study included children aged less than 18 years, having a confirmed diagnosis of epilepsy defined according to the International League against Epilepsy classification of 2017,[11] availability of an immediate caregiver for a physical or phone interview, and having regularly attended the PEC in the past six months.

We excluded those medical records that were missing the minimum acceptable data (age, dates of enrollment into the pediatric epilepsy clinic, unclear diagnosis, telephone contact).

Sample Size Calculation

The sample size was estimated using the Daniel 1999 formula for single population proportion with correction for finite population.[12] It was based on the proportion of poor seizure control among children at Mulago National Referral Hospital (MNRH) of 46.8%.[8] A sample size of 112 participants was obtained.

Study Procedures

Enrollment and Data Collection

All medical records for CWE available at the clinic were assessed for eligibility by the study team. Patient information including socio-demographic and clinical data, including diagnosis, treatment, comorbidity, and possible etiological records, was abstracted to the questionnaire. A total of 140 medical records were screened for eligibility, and only 28 participants did not meet the inclusion criteria. One hundred and twelve (112) participants were included as shown in Figure 1.

A total of 140 medical records were screened, and 112 forms were included in the study (see Figure 1). The questionnaire did not include patient identifiers like hospital patient number and the telephone contact. These were recorded on a different log for confidentiality. Following identification and screening of the patient records, we contacted the immediate caregivers for CWE through a phone call. Informed consent was obtained. Details of the current medical status of the child including seizure frequency, adherence to treatment, current dose were collected. Also, some information that may have been missing from the medical records was obtained.

Poor seizure control was defined as less than 100% seizure reduction in seizure frequency from baseline to the time of study in line with the ongoing "Aim for Zero" campaign by the Epilepsy Foundation.[13]

Standard Operating Procedures for prevention of the spread of COVID-19 were ensured by interviewing the participants and/or their caregivers by phone, which enabled data collection with no physical contact or travel.

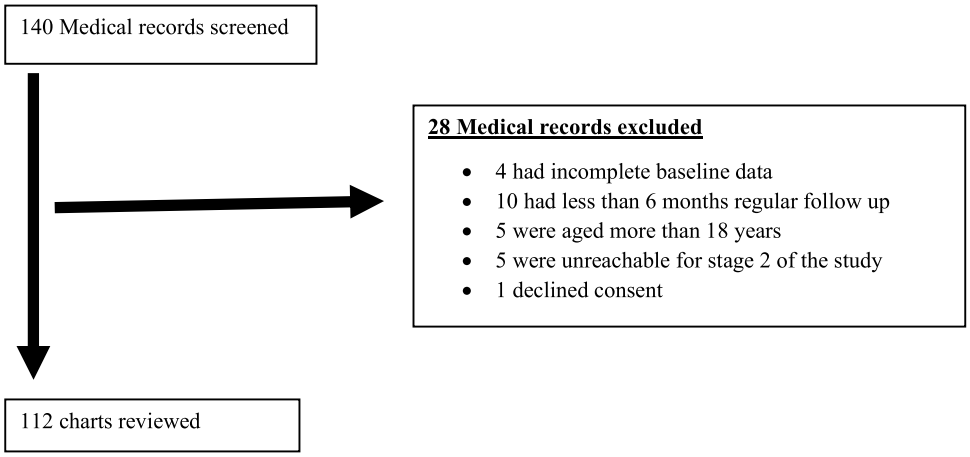

Figure 1 Flow chart of the study.

Data Management and Analysis

All data questionnaires were checked for completeness prior to entry into the database designed using EPI-DATA software version 4·2. The data were then exported to STATA version 15.0 (College Station, Texas, USA) for further cleaning and analysis. The proportion of CWE with poor seizure control was calculated as a fraction of all children enrolled in the study and expressed as a percentage with its corresponding 95% confidence interval (CI). The results were presented in the form of tables and graphs. Both bivariable and multivariable binary logistic regression analyses were done to see factors associated with seizure control status. All independent variables with p-value ≤0.2 in univariate analyses and those which were biologically plausible with poor seizure control were considered in the multivariate analysis to control for all the possible confounders. Adjusted odds ratio (AOR) with a 95% confidence interval (CI) was computed to see the magnitude of association between seizure control status and the independent variables such as age, presence of comorbidities, history of birth asphyxia, adherence to ASMs, and duration of ASM treatment, etc. Level of statistical significance was set at p–value of <0.05.

Results

Participants' Characteristics

The mean age of all the children enrolled was 7.7 years (SD± 4.3 years) with over half of them being males (53.6%). Majority of the study participants were of Ankole tribe (77.7%) residing in greater Mbarara district (88.4%) and lived with their biological parents (88.4%). Thirty-one (27.7%) of the study participants had positive family history of epilepsy. Sixteen had a history of febrile seizures during childhood. Eight of the study participants reported history of neonatal jaundice, while 12.5% and 12.5% reported history suggestive of CNS infections prior to the onset of seizures and birth asphyxia, respectively. Majority of the participants had been in the care of the clinic for more than one year, while 69.4% had ever missed a scheduled clinic visit, and 45.6% had ever missed taking their ASMs. Forty percent of the participants had associated comorbidity. Sodium valproate was the most frequently prescribed anti-seizure medication for children with epilepsy, followed by phenobarbitone, carbamazepine, and phenytoin. Other less frequently used drugs used were prednisone, lamotrigine, and levetiracetam. Only one study participant was on a three-drug regimen, compared to 9 on dual therapy, while the majority were on monotherapy (Table 1).

Common Co-Morbidities Among Children with Epilepsy at MRRH

Forty percent (40%) of all the study participants had at least one comorbidity associated with epilepsy. The majority of these children had a single comorbidity, while 17 children with epilepsy had multiple comorbidities. The most common comorbidity identified among children attending the epilepsy clinic was developmental delay/regression, then intellectual disability and cerebral palsy, as shown in the bar graph in Figure 2. Among "others" were strabismus, spinal muscular atrophy, insomnia, thyroiditis, amnesia, and multiple limb fractures.

Classification of the Seizures

Three-quarters of the children had generalized onset seizures, 23% had focal onset seizures, and 2% were unknown onset motor seizures. The expanded classification showed the most frequent type of seizure to be generalized onset motor tonic-clonic seizure, followed by other generalized onset motor seizures and then focal onset motor seizures with no awareness. The least common seizure type was the unknown onset motor seizure as shown in Figure 3.

The proportion of participants found with poor seizure control was 60.4% (95% CI 50.9–69.9), while 39.6% reported good seizure control.

Table 1 Characteristics of the Study Participants

Characteristic (*N*=112)	Frequency (*n*)	Percentage (%)
Age categories in years		
<5	37	33.0
5–9	43	38.4
10–17	32	28.6
Tribe		
Ankole	87	77.7
Ganda	9	8.0
Bakiga	8	7.1
Others	8	7.1
Religion		
Catholic	34	30.4
Protestant	60	53.6
Moslem	7	6.3
Pentecostals	11	9.8
History suggestive of birth asphyxia		
No	92	82.1
Yes	14	12.5
Unknown	6	5.4
History of status epilepticus		
No	66	58.9
Yes	46	41.1
History of head injury		
No	109	97.3
Yes	3	2.7
Associated comorbidities		
No	67	59.8
Single	28	25.0
Multiple	17	15.2
ASMs used		
Sodium valproate	48	42.9
Phenobarbitone	29	24.9
Carbamazepine	32	28.6
Phenytoin	7	6.3
Others	6	5.4
Baseline seizure frequency		
Daily	71	63.4
Weekly	12	10.7
Monthly	24	21.4
Annually	10	4.5

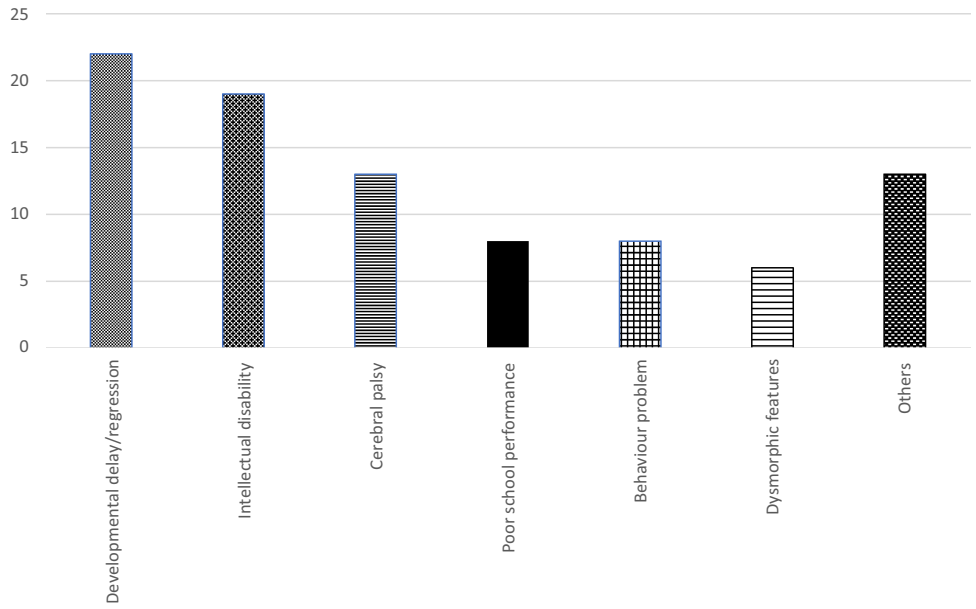

Figure 2 Frequency of comorbidities among children with epilepsy at Mbarara regional referral hospital.

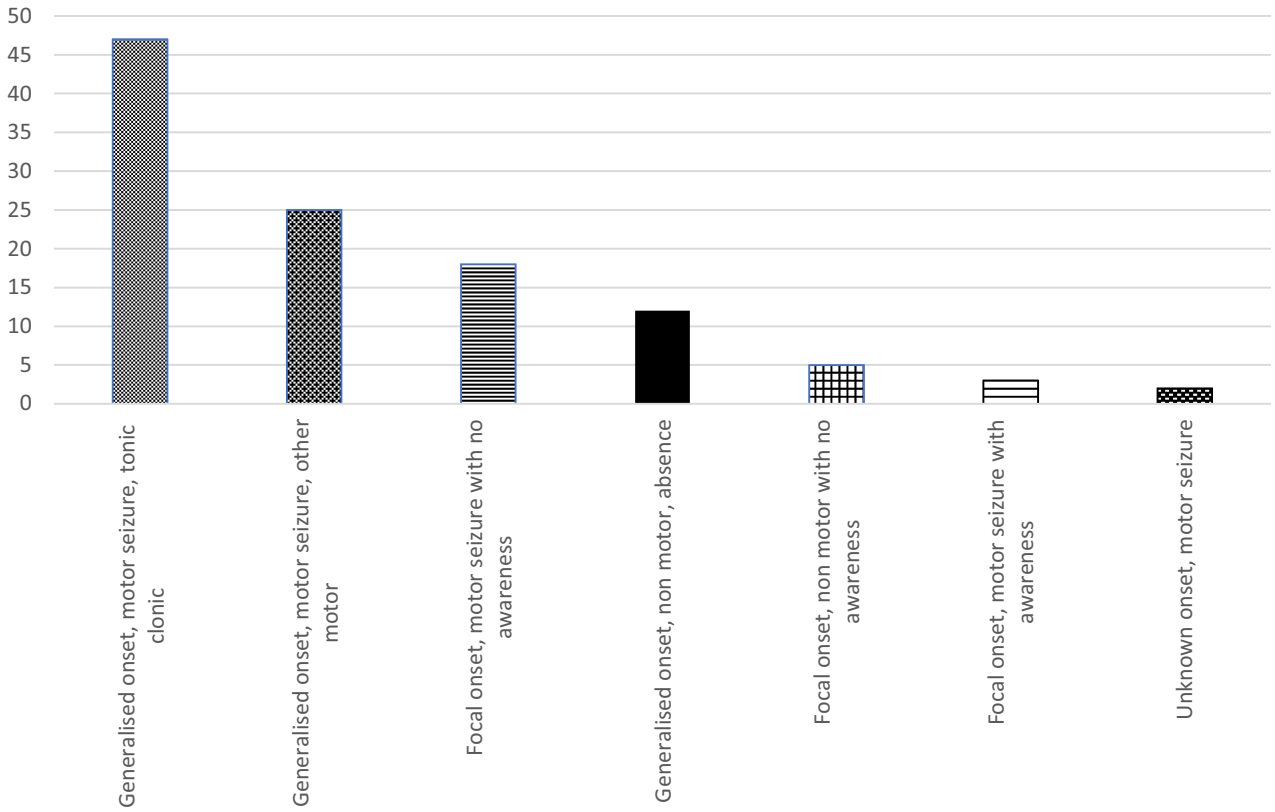

Figure 3 Classification of seizure types among children attending the epilepsy clinic at MRRH over a six-month period.

At bivariate analysis, history suggestive of birth asphyxia with unadjusted odds ratio (UOR) of 9.7 (95% CI 1.2–77.7, p=0.015) and presence of comorbidity with UOR of 3.7 (95% CI 1.3–10.2, p=0.023) were significantly associated with poor seizure control. However, type of seizure, age group of the participant, age at seizure onset, and duration of care were not associated with poor seizure control (see Table 2).

Table 2 Results of Bivariate Analysis for Factors Associated with Poor Seizure Control

Variable	Good Seizure Control *n* (%)	Poor Seizure Control *n* (%)	Unadjusted Odds Ratio (95% CI)	*P*-value
Basic seizure type				
Focal onset	10 (38.5)	16 (61.5)	1.1 (0.4–2.6)	0.888
Generalized onset	34 (40.0)	51 (60.0)	1.0	
Age groups				
<5 y	17 (46.0)	20 (54.1)	1.0	0.133
5–9 y	19 (45.2)	23 (54.8)	1.0	
10–17 y	8 (25.0)	24 (75.0)	2.5 (0.9–7.1)	
Sex				
Male	26 (43.3)	34 (56.7)	1.0	0.388
Female	18 (35.3)	33 (64.7)	1.4 (0.7–3.0)	
Duration in care				
<1 y	7 (30.4)	16 (69.6)	1.0	0.311
1 y and above	37 (42.1)	51 (57.9)	0.6 (0.2–1.6)	
Age at seizure onset				
<1 y	10 (38.5)	16 (61.5)	0.9 (0.2–3.9)	0.843
1–4 y	25 (43.1)	33 (56.9)	0.8 (0.2–2.9)	
5–9 y	5 (31.3)	11 (68.8)	1.3 (0.2–6.4)	
10–15 y	4 (39.4)	7 (63.6)	1.0	
Missed any dose				
No	18 (30.5)	41 (69.5)	1.0	0.080
Yes	23 (46.9)	26 (53.1)	0.5 (0.2–1.1)	
Missed scheduled clinic visit				
No	15 (44.1)	19 (55.9)	1.0	0.555
Yes	29 (38.2)	47 (61.8)	1.3 (0.6–2.9)	
History of febrile seizure				
No	31 (34.1)	60 (65.9)	1.0	0.034
Yes	10 (62.5)	6 (37.5)	0.3 (0.1–0.9)	
Unknown	3 (75.0)	1 (25.0)	0.2 (0.0–1.7)	
History of neonatal jaundice				
No	38 (40.0)	57 (60.0)	1.0	0.583
Yes	2 (25.0)	6 (75.0)	2.0 (0.4–10.4)	
Unknown	4 (50.0)	4 (50.0)	0.7 (0.2–2.8)	
History of CNS infection				
No	32 (38.6)	51 (61.5)	1.0	0.684
Yes	5 (35.7)	9 (64.3)	1.1 (0.8–3.7)	
Unknown	7 (50.0)	7 (50.0)	0.6 (0.2–2.0)	
History suggestive of birth asphyxia				
No	39 (42.9)	52 (57.1)	1.0	0.015
Yes	1 (7.1)	13 (92.9)	9.7 (1.2–77.7)	
Unknown	4 (66.7)	2 (33.3)	0.3 (0.1–2.2)	
Presence of comorbidity				
No	33 (50.0)	33 (50.0)	1.0	0.023
Single	6 (21.4)	22 (78.6)	3.7 (1.3–10.2)	
Multiple	5 (29.4)	12 (70.6)	2.4 (0.8–7.6)	

Abbreviations: CI, confidence interval; CNS, central nervous system.

Table 3 Results of Multivariate Logistic Analysis for Factors Associated with Poor Seizure Control

Variable	Adjusted Odds Ratio (95% CI)	*P*-value
Basic seizure type		
Focal onset	1.2 (0.4–3.7)	0.776
Generalized onset	1.0	
Sex		
Male	1.0	
Female	1.2 (0.5–3.0)	0.654
Age groups		
<5 y	1.0	
5–9 y	2.3 (0.7–7.3)	0.166
10–17 y	6.8 (1.8–26.6)	0.006
Age at seizure onset		
<1 y	4.74 (0.37–59.93)	0.229
1–4 y	3.91 (0.54–28.27)	0.176
5–9 y	3.68 (0.40–34.30)	0.252
10–15 y	1.0	
History suggestive of birth asphyxia		
No	1.0	
Yes	17.8 (1.8–176.8)	0.014
Unknown	0.3 (0.0–1.8)	0.175
Presence of comorbidity		
No	1.0	
Single	3.2 (1.0–9.9)	0.048
Multiple	2.7 (0.6–12.8)	0.200

Abbreviation: CI, confidence interval.

In the multivariate logistic regression analysis model, the odds of having poor seizure control among the adolescent age group (10–17 years) were significantly higher, with adjusted odds ratio (AOR) of 6.8 (95% CI 1.8–26.6, p=0.006). The odds of having poor seizure control were also significantly higher among participants with a comorbidity (AOR=3.2; 95% CI 1.0–9.9, p=0.048) and also those with history suggestive of birth asphyxia (AOR=17.8; 95% CI 1.8–176.8, p=0.014) (see Table 3).

Discussion

This study set out to determine the seizure control and factors associated with poor seizure control among children who had been attending the pediatrics epilepsy clinic at MRRH for at least 6 months.

We found the prevalence of poor seizure control among the participants at 60.4%, which is higher than the findings reported among children in other studies.[2,8,14] Our findings are, however, similar to the poor seizure control prevalence found among adults.[7,8]

The high prevalence of poor seizure control in this study could be due to the fact that the participants were largely from rural areas and could be having challenges in accessing ASMs and medical services. This could have been worsened by the total country lockdown due to COVID-19 at the time of the study. Limited investigative capacity including neuroimaging, which is known to influence the management, and serum drug levels at MRRH could also be contributing to the high proportion of poor seizure control because of inability to objectively monitor drug intake.

Factors Associated with Poor Seizure Control Among Children Receiving Care for at Least Six Months from the MRRH Epilepsy Clinic

Among children with epilepsy attending the MRRH clinic for at least 6 months, poor seizure control was significantly associated with history of birth asphyxia, presence of comorbidity at baseline, and being an adolescent. These have

consistently been found to be significantly associated with poor seizure control in other studies including a retrospective study done in Turkey and prospective study done in Nepal.[15,16]

History of Birth Asphyxia

Birth asphyxia is one of the most common causes of acquired structural abnormalities of the brain in LMIC like Uganda, and that increases the risk of intractable seizures.[11,17] Adverse perinatal events were also found to be associated with active convulsive epilepsy among children in a community-based study done in eastern Uganda.[4]

Adolescence

Being an adolescent was significantly associated with poor seizure control. This could be due to the endocrine, emotional, and psychological changes related to this age group, resulting in sleep deprivation, alcohol or other drug use, defaulting on medication, and stigma. All these contribute to poor seizure control. A recent study done in this same setting reported high prevalence of stigma among children with epilepsy, especially adolescents.[18]

Presence of Comorbidity

Comorbidity in patients with epilepsy is known to worsen morbidity, prognosis, and seizure control.[11] However, other factors like early age at seizure onset, seizure type, positive family history, and polytherapy were not found to be significant in our study as reported from other studies.[8,15,16,19,20] In a retrospective cohort study done in Turkey, early age at onset (below one year), multiple seizures in a day, diagnosis of specific syndrome of epilepsy, history of neonatal seizure and status epilepticus, symptomatic etiology, microcephaly, and presence of motor or mental deficiency or delay were found significantly associated with intractable seizure, while having generalized seizures was protective.[15]

Study Limitations

Only convulsive seizures as reported by the caregiver were considered, which may be subject to recall bias and uncertainty.

Some of the clinic files had incomplete medical records, and not all seizures occurring were recorded. Some of the telephone contacts were not be available online at the time of data collection despite several attempts. Some of the available telephone contacts could not be used to access the primary caregiver.

Conclusions

The proportion of poor seizure control among children with epilepsy in south western Uganda remains high. Comorbidity history of birth asphyxia at baseline and being an adolescent were significantly associated with poor seizure control among children in south western Uganda.

We recommend that clinicians assess all children with epilepsy before initiation of ASMs. Children with comorbidities, those of adolescence age, and those with history of birth asphyxia should be closely followed up to ensure appropriate seizure control.

Abbreviations

ASMs, anti-seizure medications; PEC, pediatric epilepsy clinic.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by Mbarara University of Science and Technology Research and Ethics Committee reference MUST-2021-53, received administrative approval from the hospital director of MRRH and study permit from Uganda National Council of Science and Technology reference HS1657ES. All study participants provided written informed

consent. All the methods were performed in accordance with the relevant guidelines and regulations as per the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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