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Prevalence and Factors Associated with Drug-resistant Epilepsy Among Children Attending the Pediatric Neurology Clinic at an Urban Tertiary Hospital in Uganda

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Abstract

Background: Epilepsy is among the most prevalent and serious neurological diseases. Anti-seizure medications are still the mainstay of management in most epilepsies. Globally, 10-40% of patients are estimated to have drug resistant epilepsy (DRE). However, there is limited data regarding DRE among children in low resource settings. **Objective**: This study aimed at determining the prevalence and factors associated with DRE among children with epilepsy in a large pediatric neurology clinic in Uganda. **Methods:** A cross-sectional study was performed between April and June 2023. Children aged 1 to 17 years with epilepsy, who had been on antiseizure medication (ASM) for at least 12 months, were recruited. **Results:** The prevalence of DRE was 12.2% (34/278); (95% CI: 8.6 – 16.7%). Factors associated with DRE included; multiple seizure episodes [APR=6.5, 95% CI: 3.3-17.4, P<0.0001], multiple seizure types [APR=4.4, 95% CI: 3.0-9.4, P<0.0001], diagnosis of an epilepsy syndrome [APR=3.6, 95% CI: 2.5-8.3, P=0.026], prior history of status epilepticus [APR=3.6, 95% CI: 2.7-6.1, P=0.001], focal seizure type [APR=2.3, 95% CI: 1.3-4.2, P=0.002], and symptomatic epilepsy [APR=2.1, 95% CI: 1.4-3.8, P=0.041]. **Conclusion:** The 12.2% prevalence of DRE estimated in this study is still high. Lower-level clinicians should be on higher alert for children with high risk factors for DRE like; multiple frequent seizures types, likely developmental and epileptic encephalopathies (DEE) and symptomatic epilepsy for timely referral to tertiary epilepsy specialized care. The study further underscores the need to make epilepsy syndromes part of routine epilepsy care.

Keywords: Epilepsy, Drug Resistant Epilepsy, Antiseizure medication, child neurology

Background

Epilepsy is the most common neurological disorder, affecting over 60 million people worldwide. Up to 80% live in sub-Saharan Africa and other low-resource settings (1,2). Previous studies in Uganda have indicated a prevalence of epilepsy at 10.3/1,000 (3). A systematic review and mate-analysis by Sultana et al (4) estimated the prevalence of DRE in children at 25%.

Antiseizure medications (ASMs) are the first line treatment for epilepsy, however, about 10-40% of patients still get recurrent seizures despite being on ASMs (5). The failure to achieve seizure control with two or more appropriate ASMs at adequate dosing is defined as Drug-Resistant Epilepsy (5,6). The global plan against epilepsy targets 70% of all people living with epilepsy achieving seizure-freedom through proper diagnosis and treatment (7). Drug-resistant epilepsy (DRE) predisposes the affected children to Sudden Unexpected Death in Epilepsy (SUDEP), cognitive dysfunction, physical injury, and a low quality of life. Yet, early detection and prediction of DRE is essential in determining the most appropriate treatment options and counselling (4). In Africa, many of the alternative therapies for the treatment of DRE are either not routinely available or costly (8). This treatment gap is a crucial global challenge of epilepsy care in low-and middle-income countries (LMICs).

Despite this, seizure control remains a challenge as multiple barriers impede timely and appropriate treatment. These include; the lack of specialized healthcare staff, limited investigative facilities, poor access to medication, and prohibitive costs associated with chronic treatment. These barriers subsequently lead to high seizure frequencies, misdiagnosis, or prescription of inadequate regimens, which worsens epilepsy stigma; and further widens the treatment gap (3,9).

Thus, this study aimed at determining the prevalence and factors associated with drug resistant epilepsy among children at St. Francis Hospital, Nsambya. This is the first step for advocacy to improve care of children with DRE.

Methods

Study Design: This was a cross-sectional study conducted at a pediatric neurology clinic of an urban tertiary hospital in Kampala, Uganda.

Sample size estimation and Sampling procedure: The sample size was calculated from the Fleiss formula(10).

$$N_{Fleiss} = \frac{[z_{\alpha/2}\sqrt{(r+1)\bar{p}(1-\bar{p})} + z_{\beta}\sqrt{rp_0(1-p_0)+p_1(1-p_1)}]^2}{r(p_0-p_1)^2}$$

$\mathbf{Z_{\alpha/2}}$ is standard normal value corresponding to the set confidence level; at 95% = 1.96, $\mathbf{Z_{\beta}}$ is the probability of type II error (Power of the test set at 80%), $\mathbf{p_0}$ is the proportion of outcome in unexposed group, and **r** is the

ratio of unexposed to exposed group. Using the odds ratio of 3.19 for mixed seizure types (19) and by substituting in the Fleiss formula, the sample size of 278 was considered for this study. Consecutive sampling was done during clinic days to recruit children aged 1 to 17 years, diagnosed with epilepsy and on ASM for a minimum of 12 months.

Data collection: On the clinic days, the parents/guardians of children with epilepsy and on ASMs were approached and informed about the study. Those willing to take part in the study were provided with consent forms and assent was also obtained for children aged 8 years and above. Demographic and clinical information was obtained by interviewing the parent or guardian and the responses entered in a formatted questionnaire. The children's electronic hospital records were also reviewed for any additional information recorded such as the baseline EEGs and brain MRI reports.

Eligibility criteria: All children with epilepsy between 1 - 17 years of age, on ASM for a minimum of 12 months who had been under the regular care of a specialized Pediatric Neurology Clinic for a minimum of 12 months were considered eligible for this study.

Study variables: The dependent variable for this study was DRE (failure to achieve seizure freedom after adequate use of two or more appropriately chosen and used ASM, for a minimum of 12 months. The independent variables included demographic parameters; age of the patient, Sex, age of onset of seizures, family history of epilepsy and duration of seizures before treatment initiation; Clinical characteristics; seizure frequency, type of seizures, and symptomatic aetiology and medications; duration of ASM, combination of ASM, and self – reported adherence.

Data management and analysis

The data was entered into an electronic database using Epidata 4.2 by double entry method, then later exported to SPSS Version 25 for analysis. Those with seizures after a minimum of 12 months treatment with 2 or more ASM were entered into the screen of the SPSS as ''Yes' while those with controlled seizure were entered as ''No''. Continuous variables (such as age), were summarized using frequencies, and percentages.

Bivariate and multivariate analysis were done to analyse relationships between the independent variables and the outcome (DRE). At bivariate analysis; the Pearson's Chi-square, and Fisher's exact test (for variables <5) were used. To determine the factors associated with DRE, log-binomial regression analysis was used since the prevalence rate was greater than 10%. At unadjusted analysis, the crude prevalence ratios (CPR) with their 95% confidence intervals and p-values were presented. All variables with p-values less or equal to 0.2 were selected for adjusted multi variate analysis using forward selection technique. Adjusted prevalence ratios (aPR) with their 95% confidence intervals and p-values were also presented. At multivariate analysis p-values less than 0.05 were considered statistically significant. The results were presented in percentages, figures and tables.

Results

Demographic Characteristics

Most (57.2%) of the participants were males, (159/278), and 42% (117/278) were between 1-5 years of age (Table 1). The median age of the children was 7.9 years (IQR-4-6). Only 8.6% (24/278) of the children had a positive family history of epilepsy. About half (52%) of the children (144/278) were started on ASM one month or more after seizure onset.

Clinical characteristics of the study participants

Many of the children (n=203, 73%) presented with focal seizures (Table 2). Over 50% of children (n =166, 59.7%) had symptomatic epilepsy. Majority (n =271, 97.5%) reported good adherence to their medication.

Electroencephalogram findings

The majority of the children had focal epileptogenic foci; 15 had generalized epilepsy, 3 had hypsarrhythmia, 1 had a burst-suppression pattern, and 24 had normal EEGs as shown in Figure 1. The prevalence of DRE was 12.2% (34/278); (95% CI: 8.6% – 16.7%).

Table 1: Demographic characteristics of children on ASM attending the Neurology clinic at St. Francis Hospital, Nsambya

Variable	Frequency (N=278)	Percentage (%)
Age categories (Years)		
1-5	117	42.1
6-10	75	27.0
> 10	86	30.9
Sex		
Female	119	42.8
Male	159	57.2
Family history of epilepsy		
No	254	91.4
Yes	24	8.6
Prior febrile seizures		
No	221	79.5
Yes	57	20.5
Age at onset of seizures		
0 - <1 month: Neonates	13	4.7
1 month - < 1 year: Infancy	59	21.2
1- <3: Toddler	67	24.1
3- <6: Pre-school	56	20.1
6- <12: Middle childhood	58	20.9
12- <18: Teenagers	25	9.0
Duration of seizures before treatment		
< 1 month	90	32.4
1-6 Months	144	51.8
>6 months	44	15.8
Prior history of status epilepticus		
No	155	55.8
Yes	123	44.2

Table 2: Clinical characteristics of children attending the Neurology clinic at St. Francis Hospital, Nsambya.

Variable	Frequency (N = 278)	Percentage (%)
Seizure type		
Focal	203	73.0
Generalised	40	14.4
Mixed	35	12.6
Symptomatic epilepsy		
No	112	40.3
Yes	166	59.7
Diagnosis of an epilepsy syndrome		
No	228	82.0
Yes	50	18.0
Seizure episodes		
< 3 episodes / week	111	39.9
Multiple; >3 episodes / week	167	60.1
Daily adherence to medication		
No	7	2.5
Yes	271	97.5
Duration of treatment with ASM		
6-11 months	1	0.4
12 - 24 months	199	71.3
>24 months	78	28.1

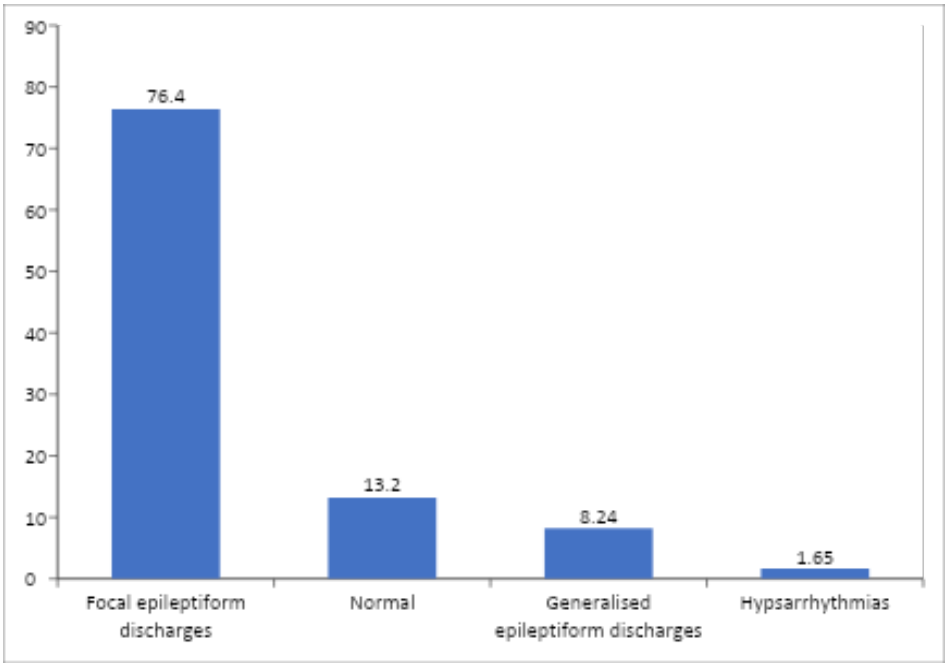

Figure 1: *Summary of Electroencephalogram (EEG) findings*

Factors associated with DRE

i) Child demographic characteristics

DRE was 3.4 times more prevalent among children with a prior history of status epilepticus [CPR=3.4, 95% CI: 2.5-5.0, P=0.002], as shown in Table 3.

ii) Clinical characteristics

Children who had multiple seizure episodes (> 3 episodes weekly) before initiation of treatment had a prevalence of DRE that was 7.8 times higher [CPR=7.8, 95% CI: 4.2-19.6, P<0.0001]. Presence of seizures of multiple seizure types was associated with a prevalence of DRE 4.6 times higher [CPR=4.6, 95% CI: 2.7-8.8, P=0.003].

Table 3: Child demographic characteristics associated with DRE at bivariate analysis

Characteristic	DRE		Crude PR	95% CI	P-value
	Yes	No			
Age categories (Years)					
1-5	21 (17.9%)	96 (82.1%)	1.0		
6-10	8 (10.7%)	67 (89.3%)	1.2	0.5-1.7	0.381
> 10	5 (5.8%)	81 (94.2%)	0.6	0.4-1.3	0.265
Sex of child					
Female	14 (11.8%)	105 (88.2%)	1.0		
Male	20 (12.6%)	139 (87.4%)	1.01	0.7-1.8	0.825
Family history of epilepsy					
No	32 (12.6%)	222 (87.4%)	1.0		
Yes	2* (8.3%)	22 (91.7%)	0.6	0.4-2.7	0.364
History of febrile seizures					
No	28 (12.7%)	193 (87.3%)	1.0		
Yes	6 (10.5%)	51 (89.5%)	0.7	0.3-2.8	0.321
Age at onset of seizures					
0 - <1 month: Neonates	1* (7.7%)	12 (92.3%)	1.0		
1 month - < 1 year: Infancy	12 (20.3%)	47 (79.7%)	1.8	0.7-2.9	0.209
1- <3: Toddler	12 (17.9%)	55 (82.1%)	1.6	0.5-2.4	0.228
3- <6: Pre-school	6 (10.7%)	50 (89.3%)	1.1	0.4-1.9	0.319
6- <12: Middle childhood	3* (5.2%)	55 (94.8%)	0.7	0.5-1.8	0.462
12- <18: Teenagers	0* (0.0%)	25 (100%)	-		
Duration of seizures before treatment initiation					
< 1 month	15 (16.7%)	75 (83.3%)	1.0		-
1-6 Months	3* (6.8%)	41 (93.2%)	1.1	0.5-1.9	0.335
>6 months	16 (11.1%)	128 (88.9%)	0.7	0.4-2.2	0.219
History of status epilepticus					
No	13 (8.4%)	142 (91.6%)	1.0		-
Yes	21 (17.1%)	102 (82.9%)	3.4	2.5-5.0	0.002

Factors associated with DRE among children with epilepsy

Children who had multiple seizure episodes (> 3 episodes /weekly) before initiation of treatment had a prevalence of DRE that was 6.5 times higher than those whose seizure frequency was less than three episodes per week [APR=6.5, 95% CI: 3.3-17.4, P<0.0001]. Presence of multiple seizure types was associated with a prevalence of DRE that was 4.4 times higher [APR=4.4, 95% CI: 3.0-9.4, P<0.0001]. The prevalence of DRE was 3.6 times more among children who had ever had an episode of status epilepticus [APR=3.6, 95% CI: 2.7-6.1, P=0.001] as shown in (Table 4,5).

Table 4: Clinical characteristics associated with DRE at bivariate analysis

Characteristic	DRE		Crude PR	95% CI	P-value
	Yes	No			
Seizure type					
Generalised	7 (17.5%)	33 (82.5%)	1.0		-
Focal	18 (8.9%)	185 (91.1%)	2.1	1.1-3.9	0.004
Multiple	9 (25.7%)	26 (74.3%)	4.6	2.7- 8.8	0.003
Symptomatic epilepsy					
No	2 (1.8%)	110 (98.2%)	1.0		
Yes	32 (19.3%)	134 (80.7%)	2.8	1.6-4.3	0.037
Diagnosis of an epilepsy syndrome					
No	19 (8.3%)	209 (91.7%)	1.0		
Yes	15 (30.0%)	35 (70.0%)	3.2	2.3-7.8	0.025
Seizure episodes					
< 3 episodes /week	1 (0.9%)	110 (99.1%)	1.0		
Multiple: >3 episodes / week	33 (19.8%)	134 (80.2%)	7.8	4.2-19.6	<0.0001
Duration of treatment with ASM					
>12 months	18 (22.8%)	61 (77.2%)	1.0		
>24 months	9 (11.5%)	69 (88.5%)	0.5	0.3-2.1	0.418
12-24 months	7 (5.8%)	113 (94.2%)	0.6	0.4-2.3	0.227
6-11 months	0 (0.0%)	1 (100.0%)	-		-

Table 5: Child demographic and clinical characteristics associated with DRE at multivariate analysis

Characteristic	DRE		Adjusted PR
	Yes	No	
History of status epilepticus			
No	13(8.4)	142(91.6%)	1.0
Yes	21(17.1%)	102(82.9)	3.6
Seizure type			
Generalised	7 (17.5%)	33 (82.5%)	1.0
Focal	18 (8.9%)	185 (91.1%)	2.3
Multiple	9 (25.7%)	26 (74.3%)	4.4
Symptomatic epilepsy			
No	2* (1.8%)	110 (98.2%)	1.0
Yes	32 (19.3%)	134 (80.7%)	2.1
Diagnosis of an epilepsy syndrome			
No	19 (8.3%)	209 (91.7%)	1.0
Yes	15 (30.0%)	35 (70.0%)	3.6
Seizure frequency			
< 3 episodes / week	1* (0.9%)	110 (99.1%)	1.0
Multiple: >3 episodes / week	33 (19.8%)	134 (80.2%)	6.5

Discussion

In this study, the prevalence of DRE among children on ASM was estimated at 12.2%. The prevalence of DRE decreased with increasing age. However, prevalence did not vary by sex, family history. This prevalence is slightly lower compared to studies conducted earlier, which reported rates ranging from 14.8% to 57% (4,11-16). This observation could partly be due to access to specialized epilepsy services by the children with epilepsy who are treated in this clinic.

In this study, the variables that were significantly associated with drug resistant epilepsy among children on ASM were; prior history of status epilepticus, the focal type of seizures, having symptomatic epilepsy, diagnosis of an epilepsy syndrome, multiple seizures types, and multiple seizure episodes prior to treatment initiation.

Prior history of status epilepticus was common (four in ten) in our study population. It was associated with a prevalence of DRE that was 3.6 times more. So, status epilepticus is an independent predictor of DRE. Our findings, consistent with various studies by Cerulli Irelli et al (17)(16), Choi et al (18) (17), and Karaoğlu et al (19) (18), showed a high occurrence of DRE following status epilepticus. In addition, a meta-analysis by Xue-Ping et al reported 11 times the occurrence of DRE in patients who had a prior history of status epilepticus (19)(20).

Children with the focal seizure type had a prevalence of DRE that was 2.3 times higher in comparison to those who had seizures with a generalized onset. This can be attributed to focal lesions with an epileptiform generator, thus the need for non-pharmacological management like epilepsy surgery as opposed to generalised seizures. Structural brain lesions, including the broad range of malformations of cortical development (MCD) and glioneuronal tumors, are among the most common causes of drug-resistant focal

epilepsy (21)(20). A study on Brain MRI findings among children with epilepsy in two urban hospital settings found that two-thirds of the children had structural brain abnormalities (21) (22).

Children who experienced multiple seizure types had a prevalence of DRE that was 4.4 times higher in comparison to those with focal seizures. Mixed seizure types are common in epilepsy syndromes, and are intractable to ASMs since multiple epileptogenic foci may be responsible thus difficult to treat. This is in agreement with other studies (19.20)

The findings of this study showed that children who had symptomatic epilepsy had a prevalence of DRE that was 2.1 times higher. Other studies also have reported symptomatic epilepsy to have an increased risk of drug resistance (23)(. The changed structure of the CNS leads to hyper-excitability. In addition, structural abnormalities damage the capillary endothelial cells that constitute the blood brain barrier resulting in over-expression of efflux transports. Some brain lesions also result in neuronal death and reactive gliosis ((24).

Vascular insults, perinatal infections, CNS infections, metabolic disorders, chromosomal abnormalities, and mesial temporal sclerosis are reported to be independent predictors of DRE (19,25).

The prevalence of DRE was 3.6 times higher among children diagnosed with an epilepsy syndrome. Mutations or polymorphisms in specific genes, such as those that encode ion channels, specific neurotransmitter receptors and molecules that have functions in intercellular communication are some of the causes of epileptic syndrome (26).One such study investigated the genetic etiology of epilepsy in a cohort of 120 children with unexplained epilepsy using whole-exome sequencing (WES); and identified the KCND3 gene. Genetic variants may also contribute to the efficacy of drug treatments for epilepsy, as well as long-term outcomes (27).

Children who had multiple seizure episodes before treatment (>3 episodes/weekly) had a prevalence of DRE that was 6.5 times higher than those whose seizure frequency was less than three per week. This is because repeated seizures produce neuronal loss and mossy fibre sprouting in the hippocampus, forming excitatory recurrent circuits (28). This finding is further consistent with the studies of Saygi et al (29), and Karaoglu et al (19), who reported a directly proportional relationship between frequency of seizures and DRE. A predictive risk model described by Huang et al following a study of 649 children <12 years with epilepsy in China, described having more than ten (11) seizures prior to initiating ASMs, as one of the significant and independent predictors of DRE (23).

In summary, all independent predictors of DRE relate to types of seizures and treatment history.

CONCLUSION

This study still showed a high prevalence of DRE (12.2%), which is consistent with earlier reports from low resource settings. Lower-level clinicians should be on higher alert for children with high risk factors for DRE like; multiple frequent seizures types, likely developmental and epileptic encephalopathies (DEE) and symptomatic epilepsy for timely referral to tertiary epilepsy specialized care. The study further underscores the need to make epilepsy syndromes part of routine epilepsy care.

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