Short-term treatment outcome of childhood epilepsy in Jos, Nigeria

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Original Article

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ABSTRACT

Background: Childhood epilepsy causes tremendous burden for the child, the family, the society and the healthcare system. While the majority of patients with epilepsy respond well to one antiepileptic drug (AED), many respond poorly to antiepileptic therapy with two or more AEDs, or develop drug-resistant epilepsy (DRE). We evaluated the short-term treatment outcomes of childhood epilepsy at a tertiary hospital in Nigeria. **Methods:** We reviewed the clinical records of newly diagnosed children with epilepsy that were commenced on AEDs from January 2011 to December 2015 and completed follow-up for at least 2 years. We evaluated their treatment outcomes and studied the association between the treatment outcomes and patients' characteristics. **Results:** Three hundred and twenty-six patients met the eligibility criteria. The remission rate was 64.1%, the relapse rate at 2 years was 5.3% while the prevalence of drug-resistant epilepsy was 19.9%. Children with focal seizures were 1.5 times more likely to achieve remission compared to those with generalized seizures (adjusted odds ratio = 1.52; $P = 0.008$). Similarly children with normal neurologic examination were about 6 times more likely to achieve remission compared to those with abnormal neurologic examination (adjusted odds ratio = 5.79; $P < 0.001$). **Conclusion:** Most children with epilepsy will achieve good seizure control if they receive appropriate treatment. We need to create more public awareness on the etiology and treatment of epilepsy in order to reduce the myths and stigma associated with the disorder and improve the long term outcome of childhood epilepsy in our community.

Keywords: Anti-epileptic drugs, children, drug-resistant epilepsy, epilepsy, remission

INTRODUCTION

Epilepsy is a common chronic brain disorder characterized by recurrent seizures that affects people of all ages, all over the world.[1,2] Epilepsy is one of the commonest reasons for referral to a neurologist and contributes about one percent of the global burden of diseases.[3] Sixty to ninety percent of the 70 million people with epilepsy worldwide reside in developing countries and constitutes about 40%–60% of patients seen at neurology clinics in sub-Saharan Africa.[4-7] In Nigeria, it is the commonest neurologic disorder affecting children and this has been attributed to the high incidence of intracranial infections and adverse perinatal events such as asphyxia and severe neonatal jaundice.[6]

The nature of epilepsy is unpredictable, leading to its characteristic interruptions in one's activity thereby altering every sphere of the patients life.[8,9] In addition, childhood epilepsy causes a tremendous burden not only for the child but the family, society as well as the healthcare system.[7,10] This is due to the significant psychosocial/neurologic morbidity, stigma and the challenges of seizure control, which often persists into adulthood affecting the quality of life of people with epilepsy.[10] Epilepsy usually presents with recurrent seizures and uncontrolled seizures can lead to secondary brain

Emeka U. Ejeliogu[1,2], Aderonke Uhunmwangho-Courage[2], Esther S. Yiltok[1,2], Mary Bok[2]

[1]Department of Paediatrics, University of Jos, Nigeria, [2]Department of Paediatrics, Jos University Teaching Hospital, Jos, Nigeria

Address for correspondence: Dr. Emeka U. Ejeliogu, Department of Paediatrics, Jos University Teaching Hospital, P.M.B. 2076, Jos, Plateau State, Nigeria.
E-mail: emekam12@yahoo.com

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damage, this makes the patients, caregivers and the neurologists to essentially focus on treating the seizures.

The goal of treatment of epilepsy includes minimizing the risk of recurrent seizures and antiepileptic drug (AED) side effects, and maintaining normal psychosocial and vocational adjustment.[11] AEDs are either used singly or in combinations. The choice of AED to be used for individual patient depends on a number of factors including the seizure type or epileptic syndrome present, the efficacy of the drug, its side effects, patient's characteristics including the presence of comorbidities and their treatability by the same AED, availability, cost and convenience of AED dosing.[11] These factors may have produced some variations in the use of AEDs. Different epilepsy types may be particularly responsive to specific AEDs but some AEDs have multiple mechanism of action with a broad spectrum of activity across a range of seizure types.

Studies have shown that not all children with epilepsy will achieve seizure remission when commenced on treatment.[12,13] While the majority of patients with epilepsy respond well to one AED, nearly up to one third of patients respond poorly to antiepileptic therapy with two or more AEDs, or develop drug-resistant epilepsy (DRE) leading to uncontrolled seizures.[13] Uncontrolled seizures and overdose of AEDs are associated with adverse effects, such as cognitive deterioration, psychosocial dysfunction, and increased morbidity and mortality.[12,13] It is important to understand the different clinical patterns of response to AED treatment, ideally by following the outcomes once the treatment has been initiated.

Children with epilepsy in developing countries are treated at all levels of healthcare delivery. It is therefore important to disseminate information and expand the literature on treatment outcomes among children with epilepsy in developing countries. This study therefore aimed to describe the treatment outcomes of childhood epilepsy at a tertiary hospital in Nigeria.

MATERIALS AND METHODS

Study design and site

This retrospective study was carried out in the pediatric neurology clinic of Jos University Teaching Hospital, Jos, Plateau State, Nigeria. The clinic runs once a week at the pediatric out-patient department (POPD) of the hospital. It receives referrals from the general pediatric out-patient clinic, general out-patient department, other pediatric specialist clinics, and from other hospitals in different parts of the state and neighboring states. It also serves as a follow-up clinic for children that were admitted for neurologic diseases in the hospital. It attends to about 40 patients every clinic day. About 50% of children attending the clinic have epilepsy.

Study population

Subjects of the study were children less than 18 years of age with newly diagnosed epilepsy that were commenced on antiepileptic drug (AED) from January 2011 to December 2015 and followed up till December 2018. Those who did not complete follow up for at least 2 years and those who did not adhere to the treatment regimen were excluded from the study.

Data collection

We used a case record form to document all relevant information of each patient. Information collected included biodata; detailed medical history: onset of seizure, type of seizure, date of commencement of AED, type and number of AEDs, adherence to AED, time of last seizure, family history of seizure; pregnancy, delivery and perinatal history; past medical history; and developmental history. Other information obtained included significant examination findings with particular emphasis on neurologic examination and results of electroencephalogram (EEG).

The treatment given to patients in the study was done as part of standard care in the management of childhood epilepsy and followed recommended guidelines.[14-16] After the diagnosis of epilepsy, an appropriate first-line antiepileptic drug (AED) was chosen, taking into account the seizure type, availability, cost and side-effect profiles. Patients were then followed up at the pediatric neurology clinic, initially 2-4 weekly depending on the distance of the patients' home to the clinic. Longer appointments were given when seizures are controlled. At every follow-up visit, clinical information and response to AED treatment were documented. Drug doses were gradually increased based on response and weight, and treatment was altered as clinically indicated. Monotherapy was used initially in all patients, additional AEDs were added if seizures were not fully controlled. Adherence to treatment regimen was monitored at the clinic using simple caregiver/patient recall.

Definitions

According to the International League against Epilepsy (ILAE)[17] revised classification of epileptic seizures, seizure types were classified into generalized or focal seizures. Generalized seizures were further categorized into motor (tonic-clonic and other motor) and non-motor types while focal seizures were categorized into awareness retained or impaired types.

Outcomes were obtained from review of medical records. In this study remission was defined as an achievement of at least one-year seizure-free period. Early remission was defined as control of seizure within one year of commencement of treatment, while late remission was defined as control of seizure after more than one year of treatment. Terminal remission was defined as remission achieved for a minimum of 2 years or at last follow up visit whichever was longer. Relapse was defined as the occurrence of repeated seizures after remission has been achieved. According to the definition proposed by the ILAE, drug-resistant epilepsy (DRE) was defined as the failure of two well-tolerated, and appropriately chosen and used AED schedules, whether as monotherapies or in combination, to achieve a sustained seizure freedom for either one year or for a period equal to three times of the pre-intervention inter-seizure time, whichever was longer.[18] Significant improvement in seizure frequency was defined as achievement of sustained seizure freedom for a period equal to three times of the pre-intervention inter-seizure time but not up to one year.

Data analysis

Data obtained was analyzed with statistical package for social sciences (SPSS) software version 20. Results were presented in descriptive statistics using tables and graph. Chi-square (for categorical variables) and Kruskal-Wallis tests (for continuous variables) were used to detect differences in clinical factors between the different outcomes. Variables that were associated with seizure remission in the bivariate analysis at $P < 0.05$ were fit into a multivariate logistic regression model and the results were expressed as adjusted odds ratio (AOR) with their 95% confidence intervals (CIs). *P*-value <0.05 was considered significant.

Ethical consideration

Ethical approval for the study was obtained from the Human Research and Ethics Committee of Jos University Teaching Hospital.

RESULTS

Four hundred and nine patients were commenced on AED within the study period. Eighty-three (20.3%) were either lost to follow up or defaulted treatment while 326 (79.7%) were retained in care and treatment. Males were 187 (57.4%) while females were 139 (42.6%). The median age of the patients at the onset of seizure was 4.7 years (interquartile range (IQR) 2.1–7.3 years) while the median age at presentation was 5.2 years (IQR 2.8–8.4 years). The mean duration of follow up was 53.2±11.8 months (range 24–93 months). Two hundred and four (62.6%) were on monotherapy, 102 (31.3%) were on dual therapy, 16 (4.9%) were on triple therapy while four (1.2%) were on quadruple AEDs. The most frequently prescribed drugs were carbamazepine (35.3%) and sodium valproate (22.7%) respectively. Figure 1 shows the etiology of epilepsy while Figure 2 shows the frequency of antiepileptic drugs used by the patients.

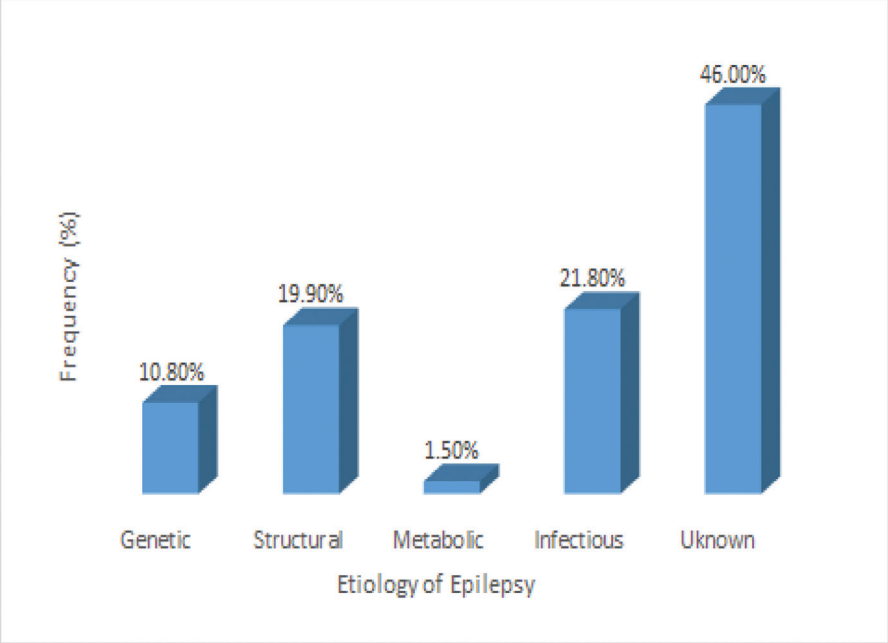

Figure 1: Etiology of epilepsy among the study subjects

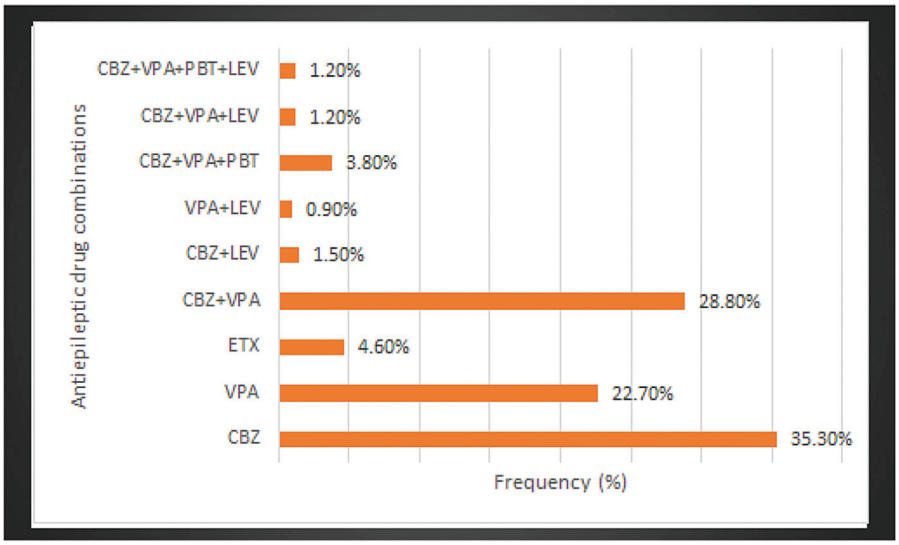

Figure 2: Frequency of antiepileptic drug therapy in the study subjects. CBZ, carbamazepine; VPA, sodium valproate; PBT, phenobarbitone; ETX, ethosuximide; LEV, levetiracetam

Outcome

Two hundred and nine (64.1%) patients achieved remission while 117 (35.9%) never achieved remission; 183 (87.6%) of the remissions were early while 26 (12.4%) were late. One hundred and sixty-five (78.9%) of the patients who achieved remission had terminal remission while 11 (5.3%) had relapse at 2 years, the remaining 33 (15.8%) had not achieved a 2 year seizure free period. Out of the 117 patients without seizure remission, 52 (44.4%) had significant improvement in seizure frequency while 65 (55.6%) did not have significant seizure control. Therefore 65 (19.9%) of the total patients had DRE.

Tables 1 and 2 show the relationship between patients' characteristics and the primary treatment outcome (seizure remission). In the bivariate model, factors that were significantly associated with remission were focal seizures, normal neurologic examination and monotherapy ($P = 0.002$, <0.001 and <0.001 respectively).

In the multivariate model, children with focal seizures were 1.5 times more likely to achieve remission compared to those with generalized seizures (adjusted odds ratio (AOR) = 1.52; 95% confidence interval (CI) = 1.14−2.55; $P = 0.008$). Children with normal neurologic examination were about 6 times more likely to achieve remission compared to those with abnormal neurologic examination (AOR = 5.79; 95% CI = 3.68–9.29; $P < 0.001$). Similarly children on monotherapy were about 7 times more likely to achieve remission compared to those on polytherapy (AOR = 7.33; 95% CI = 5.23–10.27; $P < 0.001$). Table 2 shows the multivariate logistic regression analysis of independent predictors of remission among children on AEDs.

Table 1: Relationship between patients' characteristics and treatment outcome

Characteristics	Total (%)	Remission		X^2	*P*-value
		Yes	No		
Sex					
Male	187 (57.4)	114	73	1.58	0.20
Female	139 (42.6)	95	44		
Age at onset of seizure					
<1 year	57 (17.5)	34	23	0.66	0.42
1–5 years	141 (43.3)	85	56		
6–10 years	107 (32.8)	76	31		
11–17 years	21 (6.4)	14	7		
Type of seizure					
Generalized	235 (72.1)	138	97	9.80	0.002
Focal	91 (27.9)	71	20		
Etiology of seizure					
Known	176 (54.0)	108	68	1.01	0.32
Unknown	150 (46.0)	101	49		
Neurologic examination					
Normal	257 (78.8)	196	61	75.48	<0.001
Abnormal	69 (21.2)	13	56		
Electroencephalogram					
Normal	23 (7.1)	16	7	0.16	0.69
Epileptiform	167 (51.2)	105	62		
AED Regimen					
Monotherapy	204 (62.6)	175	29	108.79	<0.001
Polytherapy	122 (37.4)	34	88		

AED, antiepileptic drug

DISCUSSION

This study was carried out to determine the treatment outcomes of newly diagnosed children with epilepsy that were commenced on AEDs. The result showed that 64.1% of the patients achieved remission while 35.9% did not achieve remission. However 44.4% of those that did not achieve

Table 2: Multivariate logistic regression analysis of independent predictors of remission

Factor	% remission	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Seizure type					
Generalized	58.72	1.00 (Ref)		1.00 (Ref)	
Focal	78.02	2.50 (1.43–4.37)	0.002	1.52 (1.14–2.55)	0.008
Neurologic exam					
Abnormal	18.84	1.00 (Ref)	<0.001	1.00 (Ref)	<0.001
Normal	76.27	13.84 (7.09–27.63)	<0.001	5.79 (3.68–9.29)	<0.001
AED regimen					
Polytherapy	27.87	1.00 (Ref)		1.00 (Ref)	
Monotherapy	85.78	15.61 (8.94–27.28)		7.33 (5.23–10.27)	

AED antiepileptic drug; OR odds ratio; CI confidence interval

remission (16.0% of total patients) had significant improvement in seizure control while 19.9% of the total patients had DRE. The remission rate obtained in this study is similar to some previous reports,[19-21] lower in some,[22,23] and higher in others.[24] Outcome of epilepsy treatment depends on several factors, these include the age at onset of seizure, identifiable causes of epilepsy, type of seizure, findings on neurologic examination and electroencephalographic features.[23-25] Younger age at onset of seizure and the presence of identifiable causes of epilepsy have been particularly associated with poor outcome. The median age of patients at onset of seizure in this study was relatively high and it could have affected the overall outcome. We did not find a significant difference in the remission rate between those with identifiable and unidentifiable etiologies, however those with unidentifiable etiologies had a slightly higher remission rate (67.3%) compared to those with identifiable etiologies (61.4%). Our study was also hospital based and that could explain the better outcome observed compared to community/ population-based studies.

The relapse rate of 5.3% at 2 years was higher than the 8.3% at 12years reported in Britain[23] but lower than the 19.5% at 2 years reported in China.[24] The differences in the relapse rates reported in the studies may be related to the differences in the selection criteria or genetic background.

DRE was observed in about 20% of our patients, this is higher than the 7% reported in Finland[25] and the 12.8% reported in China.[24] This could be as a result of the fact that many of our patients developed epilepsy from prior birth asphyxia and central nervous system (CNS) infections. Studies have shown that symptomatic epilepsies have poorer outcome compared to idiopathic epilepsy.[25,26] It is however lower than the 30% reported in Norway[26] which had a relatively younger population with a median age of 3 years. Studies have shown that onset of seizure before 3 years of age was associated with poorer outcomes.[23,25]

Those with focal seizures had significantly higher remission rate compared to those with generalized seizures. This is similar to previous reports.[25,26] Some types of generalized seizures like tonic, atonic, myoclonic and epileptic spasms are known to have poor outcomes. Most epilepsy syndromes that are associated with recalcitrant seizures usually present with generalized seizures. Also in this study, because of financial constraints, carbamazepine was used as first-line drug in the treatment of generalized seizures in some children instead of sodium valproate. This could have affected the outcome in children with generalized seizures.

We also found a significantly better seizure outcome in children with normal neurologic examination compared to those with abnormal examination findings. This is consistent with previous reports.[26,27] Abnormal brain neurons may serve as foci for epileptiform electrical discharges that may be difficult to control with AEDs. Many of the children with epilepsy in our study had birth asphyxia and CNS infection that could have led to cerebral infarction and atrophy.

In contrast to other studies,[21,25,26] we did not find any significant difference in outcome among those with normal and abnormal EEG tracings. Because of financial constraints, only 52% of our patients had EEG and it could have affected the significance of abnormal EEG tracings.Many of our patients were on polytherapy and as expected those on monotherapy had significantly better outcome. Only 27.9% of those on polytherapy achieved remission compared to 85.8% of those on monotherapy. The goal of AED therapy is to achieve full seizure control with one drug at the lowest possible dose. Monotherapy for epilepsy became standard management in the 1970s as it was recognized that polytherapy was more likely to be associated with drug toxicity. Studies have shown that AED used as monotherapy is effective in 60–70% of children.[28-30] Additional drugs in refractory patients have been shown to be only marginally beneficial.[31,32] It is also possible that because we used carbamazepine as first-line drug for some children with

generalized seizures, they did not achieve remission and therefore required combination therapy. Within the limits of financial constraints, we will endeavor to use sodium valproate as first-line drug for generalized seizures to achieve better outcome.

As at the time of this review, lamotrigine was not available at our centre. An unblinded randomised trials comparing Standard and New Antiepileptic Drugs (SANAD) Arm A found that lamotrigine was clinically better than carbamazepine, the standard drug treatment, for time to treatment failure outcomes and is therefore a cost-effective alternative for patients diagnosed with focal seizures.[33]

It is noteworthy that there was a high default rate in the study. As many as one in five patients were either lost to follow up or defaulted treatment. This is generally the case with chronic illnesses in developing countries. It is even worse with epilepsy as it is sometimes believed to be associated with spiritual attacks and therefore should not be treated with orthodox medicine. We need to create more public awareness on the etiology and treatment of epilepsy in order to reduce the myths and stigma associated with the disorder and improve the long term outcome of epilepsy in our community.

Finally, excluding the high default rate, the short-term treatment outcome of childhood epilepsy observed in this study was comparable to what was reported in other parts of the world though with a higher rate of polytherapy. This may not be obtainable at lower levels of healthcare services in the country where many children with epilepsy will be treated. Using standard guidelines in the treatment of epilepsy will generally lead to good outcome at all levels of healthcare delivery in developing countries.

This study had some limitations. Firstly it was a retrospective study and it could have affected the quality and scope of data collected. Secondly we had a high default rate of about 20%. Thirdly the sample size was relatively small. There is therefore need for large prospective multicenter studies in the African context.

The remission rate of epilepsy observed in this study was 64.1%, the relapse rate at 2 years was 5.3%, while the rate of DRE was 19.9%. Children with focal seizures and normal neurologic examination had better outcome compared to those with generalized seizures and abnormal neurologic examination. Most children with epilepsy will achieve good seizure control if they receive appropriate treatment. We need to create more public awareness on the etiology and treatment of epilepsy in order to reduce the myths and stigma associated with the disorder and improve the long term outcome of childhood epilepsy in our community.

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Authors contribution

This work was carried out in collaboration between all authors. Author EUE contributed to the concept, design, literature search, data collection and analysis, manuscript preparation, editing and review. Authors AUC, ESY and MB contributed to literature search, data collection and analysis, manuscript editing and review. All authors read and approved the final manuscript. All authors met the requirement for authorship and each author believes that the manuscript represents honest work.

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Conflicts of interest

There are no conflicts of interest.

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