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Predictors of early seizure remission in Nigerian children with newly diagnosed epilepsy

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Summary

Background: It is important to predict as soon as possible after diagnosis and starting treatment, the likely clinical course of childhood-onset epilepsy, both in terms of seizure control and even more pertinently, seizure intractability. Little is known about the factors predictive of seizure control in African children.

Methods : All consecutive cases of newly-diagnosed childhood epilepsy seen over a period of two years in the Paediatric Neurology clinic, University College Hospital, Ibadan, Nigeria were prospectively followed for a period of three years to determine seizure outcomes. Remission was defined as being seizure-free for at least two consecutive years.

Results: A total of 170 children were enrolled but 54 defaulted and were excluded from further analysis. Twenty nine (25%) attained remission while 20 (17.2%) showed signs of intractability. The remaining 67 (57.8%) showed some response to anti-epileptic drug (AED) therapy. Primary generalized epilepsy was found to be significantly associated with seizure remission and successful discontinuation of AED. Factors associated with reduced likelihood of seizure remission were remote symptomatic/cryptogenic aetiology, slow waves on electroencephalography (EEG), high seizure frequency of at least one attack/ month at presentation, failure of response to the initial AED and presence of associated neurological deficits. On logistic regression, high seizure frequency and presence of slow waves on EEG remained independent negative predictors of seizure remission.

Conclusion: About one-quarter of Nigerian children with newly diagnosed epilepsy attain early seizure remission within the first three years of AED therapy. The major predictors of poor seizure control and failure of seizure remission include high seizure frequency at presentation and presence of slow waves on EEG.

Keywords: *Predictors, seizure remission, childhood, epilepsy*

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Résumé

C'est important de prédire de façon précise après le diagnostic et la fin du traitement, la durée des symptômes cliniques du début de l'épilepsie à l'enfance inclut le contrôle des crampes et plus pertinent l'intraçabilité des crampes. Très peu est connu des facteurs précurseurs des crampes aux enfants en Africain. Tous les cas consécutif des nouveaux cas diagnostiques d'épilepsie en enfance vu durant une période de deux ans en Ciinique pédiatrique et neurologique du Centre Hospitalier Universitaire d'Ibadan, Nigeria étaient suivi pour une période de trois ans et les résultats des crampes déterminés. La rémission était définie comme étant la période sans crampes pour une période de deux ans consécutif. Au total 170 enfants étaient recrutés mais 54 échoués et étaient exclus des analyses. Trente neuf (25%) atteignaient la rémission tandis que 20 (17.2%) démontraient des signes intracables. L'épilepsie primaire généralisée était observé étant significativement associée avec les crampes de rémission et l'arrêt des médicaments antiépileptiques. Les facteurs associés avec la rémission des crampes a l'enfance étaient l'étiologie distant symptomatique/cryptogénique des ondes faibles sur l'électroencéphalographie (EEG), fréquence des crampes élevée au moins une attaque / mois a la présentation, l'échec de répondre initialement aux médicaments et la présence associé des déficits neurologiques. En utilisant la régression, la fréquence des crampes élevée et la présence des ondes sur l'EEG restaient des facteurs indépendants négatifs de la rémission des crampes. Environ un quart des enfants Nigérian ayant des cas d'épilepsie nouvellement diagnostiqués ont eu des remissions de crampes dans les trios premières années de l'usage des médicaments antiépileptiques. Les facteurs majeurs de contrôle des crampes et l'échec de la rémission des crampes incluent la fréquence des crampes élevées la présentation et la présence des ondes faibles sur l'EEG.

Introduction

Epilepsy is one of the leading non-communicable diseases worldwide, with the highest burden in the

developing countries of the world [1]. In clinical practice, it is important to predict as soon as possible after diagnosis and starting treatment, the likely clinical course of childhood-onset epilepsy, both in terms of seizure control and even more pertinently, seizure intractability and increased risk of death [2]. It is reported that as many as two of three newly treated patients with epilepsy will eventually enter remission for several years [3]. Sillanpaa and Schimd [4] have estimated that half of the patients with childhood-onset epilepsy will eventually enter remission without relapse and a fifth after relapse while one-third will have a poor long-term outcome in terms of persistent seizures after remission or without any remission ever.

Previous studies in Nigeria have shown that generalized tonic clonic seizures represent the predominant form of childhood epilepsy [5,6]. Primary generalized tonic clonic seizures are associated with an increased risk of injury and death and optimal control of these seizures is therefore important to reduce epilepsy-related morbidity and mortality [7]. Berg *et al* [8] found idiopathic generalized epilepsy and age of onset of epilepsy between five and nine years to be associated with a substantially increased remission rate.

On the other hand, symptomatic aetiology, positive family history of epilepsy, slowing on electroencephalography and initial seizure frequency negatively influenced the probability of entering remission [8]. Danesi [9] in a prospective review of adult Nigerian epileptics found the prognosis of seizure control to be more favourable in generalized than partial epilepsy, in patients with onset of seizure after the age of ten years, patients with less frequent seizures, in those who started anti-epileptic drug (AED) treatment within two years of onset of seizures and in patients who had an initial normal EEG. Initial seizure frequency has been reported as a predictor of seizure control in previous studies [10,11] but Spooner *et al* [12] in a review of a cohort of 77 children with new-onset temporal lobe epilepsy found lesions on magnetic resonance imaging (MRI) and not seizure frequency to be predictive of seizure outcome.

This study set out to evaluate the factors predictive of early seizure remission in a cohort of Nigerian children with newly diagnosed epilepsy seen at the paediatric neurology clinic of the University College Hospital, Ibadan, Nigeria. The findings would be useful in identifying children who are more likely to be at risk of intractable seizures and would help to optimize treatment.

Materials and methods

The study site was the paediatric neurology clinic, University College Hospital, Ibadan, Nigeria and the subjects were children with newly diagnosed epilepsy seen in the clinic over a period of two years, January 2005 to December 2006. Epilepsy was defined as separate occurrence of two or more unprovoked seizures, not diagnosed as neonatal or febrile seizures [13]. The diagnosis of epilepsy in the children was based on history from a reliable eye witness account, the patient's account and the electroencephalography (EEG) findings. Seizure types and epilepsy disorders in these patients was based on the International classification of epileptic seizures, epilepsies and epileptic syndromes of the League against Epilepsy (ILAE) (1993) [13]. The epilepsies were further classified as idiopathic, remote symptomatic and cryptogenic. Idiopathic refers to those epilepsies with a likely genetic cause, remote symptomatic refers to those following a prior brain injury while epilepsies with suspected but not proven prior brain injury were classified as crytogenic [13]. All were prospectively followed for a period of three years. Informed consent was obtained from all the caregivers of children with epilepsy who made their first visit to the paediatric neurology clinic during the study period and had never been on anti-epileptic drugs (AED). The following information was obtained using a structured questionnaire: name, age, gender, source of referral and parents' level of education and occupation. Detailed history of the seizures was taken and this included the age at first seizure, detailed eye witness account of seizure activity, frequency of seizures, duration of epilepsy before commencement of AED and family history of epilepsy. Detailed history of the pregnancy, birth, neonatal events, development and past medical history was taken. All the children were carefully examined with particular attention to the central nervous system. Presence of other features of neurological impairment was documented.

All the children had EEG done. Neuroimaging studies were requested in those with focal epilepsy and symptomatic epilepsy. All were placed on AED based on the standard hospital protocol for treatment of epilepsy and followed up with 2monthly clinic visits over a period of three years. The following parameters were assessed at each clinic visit: drug compliance, frequency of seizures, total duration of seizure-free periods, any response to AED, date of last seizure,

any need for change of AED. Compliance was determined by questioning the patient: "have you taken your drugs regularly?" and was termed good if the patient answered: "yes, according to the given instructions". The response was further validated by asking for a description of the drugs, the doses administered and the last time the drug was taken. The caregivers were also requested to show the AED to the doctor in those who brought theirs to the clinic. There are no facilities for monitoring AED levels in the blood or urine at the centre and this could not be done as objective evidence of compliance to AED therapy. Those who remained seizure-free for at least two consecutive years were classified to be in remission [8] and their AEDs were discontinued over a period of 3-4months and the outcome was recorded. Relapse was defined as recurrence of seizures after remission [8].

Data was entered into a microcomputer using SPSS 17 for windows software and checked for errors by generating frequencies of all variables. Data summarization was done using proportions, means, median and standard deviation depending on the units of the variables. Association between categorical variables was tested using the Chi square test and the level of significance was set at <0.05. Binary logistic regression analysis was used to identify factors that were predictive of seizure remission.

Results

A total of 170 children with newly diagnosed epilepsy were enrolled into the study; 99 males and 71 females, with a male to female ratio of 1.4 to 1. Their ages ranged from 4 months to 13 years with a mean (SD) of 63.5 (SD= 42.6) months. The mean age at first epileptic seizure was 38.6 (SD= 36.2) months. Table 1 shows the distribution of the age at first epileptic seizure. A history of neonatal seizures was obtained in 11 (6.5%) of the children. At presentation, 118 (69.4%) had severe epilepsy which was defined as seizure frequency of at least one episode per month.

Table 1. Age distribution at first epileptic seizure in 170 Nigerian children with newly diagnosed epilepsy

Age at first epileptic seizure (months)	Number of cases	%
>1- 12	53	31.2
13-60	79	46.5
61-120	30	17.6
>120	8	4.7
Total	170	100.0

A positive family history of epilepsy was found in 24 (14.1%) cases. Epilepsy was classified as idiopathic in 69 (40.6%), remote symptomatic in 81 (47.6%) and cryptogenic in 20 (11.8%). The underlying risk factors for epilepsy in the remote symptomatic group were intracranial infections in 30 (37.0%), perinatal asphyxia in 27 (33.3%), traumatic head injury in 9 (11.1%), congenital brain malformations in 4 (4.9%), neurocutaneous syndrome in 4 (4.9%) and cerebrovascular accidents in 3 (3.7%), intrauterine infections in 2 (2.5%) and bilirubin encephalopathy in 2 (2.5%). Generalized epilepsy was the most predominant form seen in 91 (53.5%) cases, while 60 (35.3%) and 19 (11.2%) had localization-related epilepsy and specific epileptic syndromes respectively. Table 2 shows the pattern of seizures and the epileptic syndromes in the 170 children enrolled into the study.

Table 2: Pattern of seizures and epileptic syndromes in 170 children with newly diagnosed epilepsy

Seizure type	Number of cases	%
Generalized tonic/clonic	70	41.2
Partial secondarily generalized	41	24.1
Complex partial	15	8.8
Absence	7	4.1
Atonic	6	3.5
Mixed	6	3.5
Simple partial	4	2.4
Myoclonic	2	1.2
Epileptic syndromes		
Rolandic epilepsy	13	7.6
Infantile spasms	4	2.4
Lennox Gastaut syndrome	2	1.2
Total	170	100.0

In addition to epilepsy, 74 (43.5%) children had other associated neurocognitive impairments and motor disabilities. The most frequent impairments identified were cerebral palsy in 42 (24.7%), mental retardation in 42 (24.7%), and hearing and visual impairments in 14 (8.2%) and 13 (7.6%) respectively. Some children had multiple associated impairments.

Fifty four (31.8%) of the 170 children defaulted from follow up and were not compliant with therapy; these were therefore excluded from further analysis. Of the remaining 116 (68.2%) children, 81 (69.8%) were on monotherapy and the most frequently used AEDs were carbamazepine in 63 (77.8%), sodium valproate in 12 (14.8%), phenobarbitone in 4 (4.9%) and phenytoin in 2 (2.5%). The remaining 35 (30.2%) children were on polytherapy with varying

Table 3: Bivariate associations between seizure remission and predictor variables

Variable	Remission			P-value
	Yes n(%)	No n(%)	Total	
Age at first epileptic seizure				
First year of life	6 (16.7)	30(83.3)	36	0.576
After the first year of life	13(16.3)	67(83.8)	80	
Seizure frequency				
≥ 1 attack/month	10 (12.0)	73 (88.0)	83	0.046
< 1 attack/month	9 (27.3)	24 (72.7)	33	
Primary generalized epilepsy				
Yes	10 (29.4)	24 (70.6)	34	0.018
No	9 (11.0)	73 (89.0)	82	
Slow waves on EEG				
Yes	1(2.3)	43 (97.7)	44	<0.001
No	15 (27.8)	39 (72.2)	54	
Other neurocognitive deficits present				
Yes	4 (7.5)	49 (92.5)	53	0.016
No	15 (23.8)	48 (76.2)	63	
History of neonatal seizures				
Yes	2 (25.0)	6 (75.0)	8	
No	17 (15.7)	91 (84.3)	108	0.388
Response to initial AED				
No	2 (4.2)	46 (95.8)	48	0.004
Yes	16 (23.5)	52 (76.5)	68	
Aetiology of epilepsy				
Idiopathic	10 (33.3)	24 (66.7)	34	<0.001
Remote symptomatic/ cryptogenic	9 (21.1)	73 (69.1)	82	

combinations of first-line AEDs and 8 of them on a combination of first line AED and second-line AEDs namely vigabatrin (2), clonazepam (3) and lamotrigine (3). By the end of the first year of commencement of AED, 47 (40.5%) of the children had required a change from the first AED prescribed on account of sub-optimal seizure control.

Ninety six (82.8%) of the 116 children showed some improvement on AED therapy while 20 (17.2%) did not show any appreciable response to AED. Of the 20 who did not respond to AED, 4 (20%) had idiopathic epilepsy while 16 (80%) were in the symptomatic/cryptogenic group. Nineteen (16.4%) of the 116 children had smooth-sailing epilepsy with no seizure recurrence after commencement of AEDs. By the end of 3years of follow up, 29 (25.0%) had achieved remission with a seizure-free period of at least two consecutive years and their AEDs were discontinued. Twenty one (18.1%) were successfully weaned off AED and remained free of seizures, but seizures relapsed in 8 (6.9%) when AEDs were tailed off and these had to be recommenced on medications. Improvement in seizure control was classified as mild in 24 (20.7%), with the longest seizure-free period of 3-6months, moderate in 22 (19.0%) with a longest seizure-free period of 7-12 months and marked in 50 (43.1%) with a longest seizure-free period greater than 12months during the 3year period of follow up.

Children with other associated neurocognitive impairments were less likely to achieve remission and be successfully weaned off AED (p= 0.016, OR 0.261, 95% CI 0.081-0.844). Primary generalized epilepsy was found to be significantly associated with seizure remission and successful discontinuation of AED (p<0.001, OR 7.841 95% CI 2.659-23.120). Presence of slow waves on EEG was significantly associated with a lesser likelihood of seizure remission (p<0.001, OR 0.060, 95% CI 0.008 -0.479). Children with severe seizures at presentation, defined as a seizure frequency of at least one episode per month were less likely to achieve seizure remission and successful discontinuation of AED (P=0.007, OR 0.105, 95% CI 0.358-2.972). There was no statistically significant relationship between the likelihood of seizure remission and age at first epileptic seizure (p=0.576, OR 1.031, 95% CI 0.358-2.972), family history of epilepsy (p=0.411, OR 1.466, 95% CI 0.367-5.848) and a history of neonatal seizures (p=0.338, OR 1.784, 95% CI 0.332-9.593). Poor response to the first AED necessitating a change of AED therapy was associated with a reduced chance

of attaining seizure remission in the first 3years of treatment (p=0.007, OR 3.007, 95% CI 1.292-6.998).

Table 4: Logistics regression analysis of seizure remission on predictor variables

Variable	â	Odd's ratio	95% Confidence Interval	P-value
Presence of associated neurocognitive impairments	-7.42	0.476	0.130-1.745	0.263
Primary generalized seizure	0.846	2.330	0.667-8.139	0.185
Slow waves on EEG	-2.165	0.115	-.034-0.387	<0.001
Frequent seizures ≤ 1/month	-1.859	0.156	0.046-0.532	0.003
First epileptic seizure in first year of life	0.046	1.048	0.306-3.558	0.941

Table 3 shows the bivariate associations between seizure remission and predictor variables.

After adjusting for presence of co-morbidities and primary generalized seizure, seizure frequency of at least one episode per month and presence of slow waves on EEG remained independent negative predictors of seizure remission with affected children being less likely to achieve seizure remission (Table 4).

Discussion

It is reported that about three-quarters of children with newly diagnosed epilepsy achieve a substantial period of remission soon after initial diagnosis [2-4,14,15]. In this study, only one-quarter of the children studied entered remission during the three year period of follow up, although 50 (43.1%) of the children showed marked response to AED with a seizure-free period greater than 12 consecutive months. This is considerably lower than the 2-year remission rate of 74% reported by Berg *et al* [8]. The major reason for this disparity may be the duration of follow up which differed in the two studies. We followed our patients up for a period of three years but the period of follow up in the study by Berg *et al* [8] was 2-8 years, with a median of 5.3years. The authors [8] found a median time to achieve remission of 2.3 years, with a range of 2 to 6 years, and the probability of a two-year remission (with 95% confidence intervals) at 24, 30, 36, 48, 60, 72 and 84 months after diagnosis was 7% (5-9%), 40% (36-44%), 50% (46-54%), 66% (62-70%), 73% (69-77%), 81% (77-85%) and 84% (80-88%) respectively. Sillanpaa and Schmidt[4] in a 40-year follow up study of children with newly diagnosed epilepsy found that failure to enter remission early in the course of treatment does not predict a long-term poor outcome. The Dutch study of Epilepsy in Childhood followed 453 newly diagnosed children and found out that 64% were no longer receiving medication 5 years later [15]. These therefore, suggest that with a longer period on AED therapy, many more of the children would enter remission.

It is known that when AEDs are started, most children will still have more seizures and only 20% have smooth-sailing epilepsy that is, become seizure-free immediately after starting medication and are able to discontinue medication without having another seizure [16]. Nineteen (16.4%) of the children in our study did not have any more seizures after commencement of AED and remained free of seizures even after AED was discontinued. In the study by Sillanpaa and Schmidt [4]; 23 (16%) of 144 children with newly diagnosed epilepsy had early remission which continued, uninterrupted by relapse to terminal remission. The proportion of children with "smooth-sailing" epilepsy found in our study is thus consistent with what is documented in literature. By the end of the first year of initiating treatment, the initial AED had been changed in 47 (40.5%) children on account of sub-optimal seizure control. It is estimated that only 50% of children with epilepsy continue to receive the same medication 1year after initiating treatment [17-19]. This has significant implications for counselling at the commencement of AED therapy, particularly in developing countries of the world where poverty and harmful cultural beliefs abound and patients therefore readily default from orthodox medical care.

Twenty (17.2%) of our patients did not show any appreciable response to AED treatment and continued to have frequent seizures despite use of multiple AEDs. Although the definition of intractability varied widely in previous studies [3,20,21], these children qualify to be labeled as having intractable epilepsy, with failure of seizure remission on a combination of 2 or three AEDs, a seizure frequency of at least one attack in 2months

and failure to achieve a seizure-free period of at least 3months over the three-year period of adequate treatment and follow up. Although the definition of intractability in the two studies differed, Berg and Shinar [21] reported intractability in 9.8% of the 613 children studied while Camfield and colleagues [16] reported intractability in 8% of 511 children. Our study found a higher proportion of children labeled as intractable but it is generally known that intractability for an individual is difficult to predict before several years of AED therapy and tends to decrease with prolonged follow up [22]. Symptomatic cause is a major factor in intractability [22] and 80% of our patients with intractable epilepsy were in the remote symptomatic/cryptogenic group.

The independent factors predictive of seizure remission in the study were presence of slow waves on electroencephalography (EEG) and a high seizure frequency at presentation. Slow waves on EEG represent EEG abnormalities that are classified as non-specific because they do not reflect an epileptogenic disturbance of neuronal function. Slow waves on EEG are however important as they may help to identify associated static or reversible encephalopathies, underlying focal cerebral lesions or progressive neurologic syndromes and have been shown to be predictive of poor seizure control and intractability [7,23,24]. Children who had frequent seizures, with a seizure frequency of at least one seizure attack per month were found to be less likely to enter remission. Initial seizure frequency appears to be a predictor for seizure control in several community or population-based studies of childhood-onset epilepsy [8,10] and it has been reported that high initial seizure frequency is more common in cases of drug resistant epilepsy.

Conclusion

About one-quarter of Nigerian children with newly diagnosed epilepsy attain early remission. Factors associated with poor seizure outcome include a remote symptomatic or cryptogenic aetiology, presence of other neurological deficits, a high seizure frequency of at least one attack per month, poor response to the initial AED and presence of slow waves on EEG. Primary generalized epilepsy is associated with a favourable prognosis. The factors that are independent negative predictors of seizure remission are slow waves on EEG and a high seizure frequency at presentation.

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