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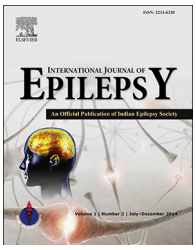

Original Article

Time to treatment predicts seizure outcome in a high-treatment gap epilepsy population

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ABSTRACT

Objectives: To investigate the relationship between time to antiepileptic drug (AED) treatment (TTT) and seizure outcome in a high treatment gap sub-Sahara African setting.
Methods: Clinical and demographic characteristics of 72 adults with epilepsy aged 18–75 years were obtained. We estimated TTT as the difference between the duration of epilepsy and the duration of treatment. Indices of clinical outcome including seizure severity and 6-month disease remission were documented. The effects of TTT and other clinical and demographic characteristics on clinical outcomes were tested using bivariate and logistic regression analyses.
Results: Forty (55.6%) of the participants initiated treatment within 5 years of seizure onset (TTT ≤ 5 years) while 32 (44.4%) initiated treatment after 5 years (TTT > 5 years). There was moderate to strong correlation between TTT and age of onset ($p = .009$), age at treatment initiation ($p = .026$), duration of epilepsy ($p = .000$), and seizure severity ($p = .020$). The TTT > 5 years group had an earlier mean age of onset ($p = .015$) and higher seizure severity score ($p = .001$) and were less likely to be in 6-month disease remission ($p = .014$). Time to treatment ≤5 years was the only independent predictor of lesser seizure severity (OR = 0.163, 95% CI = 0.041–0.649) and better 6-month remission (OR = 0.154, 95% CI = 0.031–0.770) after adjusting for age of onset, duration of epilepsy, and number of AEDs.
Conclusion: Delayed treatment initiation is common in our sample and independently associated with poor seizure outcome.

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1. Introduction

Epilepsy is associated with psychosocial consequences, such as social stigma and discrimination, which are often severe enough to force people with the disorder ''into the shadows''.[1] Consequently, a substantial number of people with epilepsy often remain undiagnosed and untreated.[1] This is partly responsible for the wide epilepsy treatment gap in some African countries estimated to be up to 95%.[2] Without treatment, the probability of long-term remission is 30–42%[3–5] while with treatment, it is 65–80%.[6–10] A large proportion of people with untreated epilepsy will therefore experience continued seizures and this may have enormous implications for outcome when treatment is instituted eventually.[4]

Studies of the prognosis of epilepsy have demonstrated a significant increase in risk for seizure recurrence with increasing numbers of seizures[11] and a decrease in the likelihood of remission following treatment in individuals with large numbers of seizures prior to treatment.[12–14] Continued occurrence of seizures also has the facility to cause changes to the ultrastucture of the brain which are not found in people with well controlled epilepsy.[15,16] It then follows that the time spent with untreated epilepsy may be as important as the absolute duration of the disease and the duration of its treatment in the prediction of long-term clinical outcomes in epilepsy.

However, while many studies have related the durations of epilepsy and its treatment and other time-related factors to the outcome of epilepsy, the time interval between epilepsy onset and treatment initiation has not been related to epilepsy outcome in many studies, particularly in wide treatment gap settings. In this study, we therefore, investigated the demographic and clinical factors associated with prolonged time ''in the shadows'' and its predictive effect on select clinical outcome indices of treated epilepsy.

2. Materials and methods

2.1. *Participants and procedures*

A total of 72 adult patients between the ages of 18 and 75 years with a diagnosis of epilepsy seen at the neurology clinic of the University College Hospital, Ibadan, Nigeria, were enrolled into the study. Criteria for inclusion in the study were a history of two or more unprovoked seizures and informed consent. Demographic data including age, sex, marital status, highest formal educational level, employment status, average monthly income, ethnicity, and religion were obtained. Disease-related variables including seizure frequency and type, etiology and class of epilepsy, duration of epilepsy, duration of treatment, and number of antiepileptic drugs (AEDs) were also obtained. Classification of epileptic seizures were based on the International League Against Epilepsy (ILAE) guidelines.[7,17] The indices of clinical outcome used were seizure severity, seizure freedom, and number of antiepileptic drugs. Time to treatment (TTT) (in years) was estimated from the difference between the duration of the disease and the duration of treatment. TTT was then dichotomized into ≤5 years (TTT ≤ 5 years) and >5 years (TTT > 5 years). All data were obtained from the patients and their case records.

The subjects were stratified into four seizure-specific severity groups (seizure free, low, moderate, and high seizure severity categories) based on the number of seizures in the previous 6 months and seizure type. This was a modification of the criteria for seizure-specific categorization of severity of epilepsy developed by Devinsky et al.[18] This scheme stratifies patients into seizure severity categories based on the number of seizures in the previous year and seizure type such that low, moderate, and high seizure severity levels for simple partial and absence seizures correspond to 1–20, 21–100, and 101–200 seizures, respectively, in the previous year. For complex partial seizures, low, moderate, and severe seizure severity correspond to 1–4, 5–12, and 13–24 seizures, respectively in the previous year, while for generalized tonic-clonic seizures, they correspond to 1, 2–4, and 5–12 seizures, respectively in the previous year. In this study, this was modified by obtaining seizure frequency data in the previous 6 months, therefore, half the seizure frequencies required were used for categorization into seizure severity groups. A score of zero was assigned to seizure freedom, while scores of 1, 2, and 3 were assigned to the low, moderate, and seizure severity levels, respectively.

2.2. *Statistical analysis*

The demographic and clinical characteristics of the subjects were summarized using the Student's *t*-test and univariate chi-square test. Analysis of the relationship between dichotomized TTT and continuous variables was done using Student's *t*-test. Relationship between dichotomized TTT and categorical variables was analyzed using univariate chi-square test. To determine the independence of TTT in the prediction of seizure severity and seizure freedom, a binary logistic regression model was constructed. For this purpose, seizure severity was dichotomized with scores of 0 and 1 in a group and 2 and 3 in another group. A 5% statistical significance level was chosen. The Statistical Package for the Social Sciences (SPSS), version 16 (SPSS Inc., Chicago, IL, U.S.A.) was used for all analyses.

2.3. *Ethical clearance*

Ethical clearance was obtained from the Health Research Ethics Committee of the University of Ibadan/University College Hospital, Ibadan, Nigeria.

3. Results

3.1. *Demographic and clinical characteristics of the study participants*

The mean age of the participants was 33.7 years (range 18–75 years) and 55.6% were male. About 87% were either students or in paid employment with slightly more than half earning up to 40 dollar equivalent a month (about 60% earned up to a dollar a day) (Table 1). Focal seizures were the most common seizure type (88.9%) with dyscognitive symptoms

Table 1 – Demographic and clinical characteristics of the study participants.

Characteristic	Value
Demographic data	
Age (years, mean ± SD)	33.7 ± 13.8
Sex (male)	40 (55.6)
Educational attainment {*n* (%)}	
Tertiary education	29 (40.8)
Married {*n* (%)}	
Currently married	23 (32.4)
Employment status {*n* (%)}	
Employed/student	62 (87.3)
Unemployed	6 (8.5%)
Retired	3 (4.2)
Missing	1 (1.4)
Median monthly income (Dollar equivalent)	40
Clinical data	
Age of onset (years) (mean ± SD)	18.7 ± 15.8
Duration of epilepsy (years) (mean ± SD)	15.2 ± 15.2
Duration of treatment (years) (mean ± SD)	7.8 ± 6.6
Time to AED treatment (years) (mean ± SD)	7.9 ± 8.5
Putative cause {*n* (%)}	
Unknown	40 (56.6)
Trauma	15 (20.8)
Perinatal brain injury	3 (5.6)
Cerebrovascular disease	8 (11.1)
Others	5 (6.5)
Seizure type, *n* (%)	
Focal seizure only	6 (8.3)
Evolving into bilateral convulsive seizures	58 (80.6)
Generalized seizures	8 (11.1)
Seizure severity (mean ± SD)	3.0 ± 1.2
6-Month remission, *n* (%)	
Yes	14 (20.3)
Number of AEDs, *n* (mean ± SD)	1.3 ± 0.6

accounting for 66.6% of all cases. Most (80.5%) of the focal seizures evolved into bilateral convulsive seizures. The mean (±SD) age of onset of epilepsy was 18.7 years (±15.8 years) with childhood-onset epilepsy accounting for 51.4% of all cases. The mean disease duration was 15.2 years (range 2–48 years) while the mean duration of treatment was 7.8 years (range 1–29 years). Mean time to AED treatment was 7.9 (±8.9) years. About a quarter of the participants were taking more than one AED, while about 20% had been in remission for at least 6 months (Table 1). None of the participants were on any other form of treatment for epilepsy.

Forty (55.6%) of the participants initiated AED therapy within 5 years of the onset of the disease; of these, 27 (37.5%) initiated AED therapy within the first year. Thirty-two (44.4%) of the participants initiated treatment after 5 years of the onset of the disease. Of these, 21 (29.2%) initiated treatment after 10 years of the onset of the disease.

3.2. *Relationship between participants' demographic and clinical characteristics, TTT, and seizure outcome variables*

There was moderate to strong correlation between time to AED treatment and age of onset ($p = .009$), age at treatment initiation ($p = .026$), duration of epilepsy ($p = .000$), and seizure severity ($p = .020$) (Table 2). When TTT was dichotomized using a 5-year cut-off, there were significant differences between the group of participants that initiated AED treatment within 5 years (TTT ≤ 5 years) and the group that initiated after 5 years (TTT > 5 years). While the two groups had no age or gender differences, the TTT ≤ 5 years group were less likely to be unemployed compared with the TTT > 5 years group ($p = .004$). Otherwise, there were no other demographic differences between the two groups (Table 3). Mean time to AED treatment was 1.8 (±1.4) years in the early treatment group (TTT ≤ 5 years) compared to a mean of 15.6 (±7.4) years in the late treatment group (TTT > 5 years) ($p = .000$). Participants in the late treatment group (TTT > 5 years) were much younger at disease onset compared with the early treatment group ($p = .047$). The TTT > 5 years group had epilepsy for a mean duration of 21.2 years compared with the TTT ≤ 5 years group, which had the disease for a mean of 10.3 years ($p = .000$). They did not differ in duration of treatment ($p = .060$). The TTT > 5 years group had a higher mean seizure severity score ($p = .001$) and were less likely to be seizure-free in the previous 6 months ($p = .007$) compared with the TTT ≤ 5 years group. There was no significant difference in age at treatment initiation ($p = .132$), putative cause ($p = .787$), seizure type ($p = .169$), or numbers of AEDs ($p = .169$) between the TTT ≤ 5 years and the TTT > 5 years group (Table 4). A logistic regression of time to AED treatment, age of onset, duration of epilepsy, number of AEDs, with seizure severity as the dependent variable revealed shorter time to AED

Table 2 – Correlation between time to treatment and participants' clinical and demographic data.

Variable	*r*	*p*
Age	.224	.059
Monthly income	−.018	.892
Age of onset (mean ± SD)	−.304	.009
Age at treatment initiation (mean ± SD)	.262	.026
Duration of epilepsy (mean ± SD)	.739	.000
Duration of treatment (mean ± SD)	−.129	.280
Seizure severity	.287	.020
Number of AEDs (mean ± SD)	.137	.263

Table 3 – Comparison of demographic characteristics between subjects who initiated treatment within 5 years and those who initiated after 5 years of the onset of epilepsy.

Characteristic	TTT ≤ 5 years	TTT > 5 years	*p*
Frequency, *n* (%)	40 (55.6)	32 (44.4)	–
Demographic			
Age (years) (mean ± SD)	32.6 ± 15.0	35.0 ± 12.2	.472
Sex (male), *n* (%)	20 (52.6)	20 (58.2)	.641
Educational attainment, *n* (%)			
Tertiary education	19 (65.5)	10 (34.5)	.060
Marital status, *n* (%)			
Married	12 (31.6)	13 (39.4)	.619
Employment status, *n* (%)			
Employed/student	38 (63.1)	24 (38.7)	
Unemployed	0 (0.0)	6 (100.0)	.004
Retired	1 (33.3)	2 (66.7)	

TTT, time to treatment.

Table 4 – Comparison of disease characteristics between subjects who initiated treatment within 5 years and those who initiated after 5 years of the onset of epilepsy.

	TTT ≤ 5 years	TTT > 5 years	*p*
Age of onset (years) (mean ± SD)	22.7 ± 17.3	13.7 ± 11.8	.015
Age at treatment initiation (years) (mean ± SD)	23.5 ± 17.1	28.9 ± 11.5	.132
Initiation <16 years vs ≥16 years, *n* (%)			
<16 years	16 (72.7)	6 (27.3)	.052
≥16 years	24 (48)	26 (52)	
Time to AED treatment (years) (mean ± SD)	1.8 ± 1.4	15.6 ± 7.4	.000
Duration of epilepsy (years) (mean ± SD)	10.3 ± 7.3	21.2 ± 9.8	.000
Duration of treatment (years) (mean ± SD)	9.1 ± 7.5	6.1 ± 5.1	.055
Putative cause, *n* (%)			
Unknown	22 (55.0)	18 (45)	
Trauma	7 (46.7)	8 (53.3)	.787
Perinatal brain injury	2 (50.0)	2 (50.0)	
Cerebrovascular disease	6 (75.0)	2 (25.0)	
Others	3 (66.7)	2 (33.3)	
Focal seizures, *n* (%)	32 (84.2)	32 (94.1)	.169
Seizure severity (mean ± SD)	2.5 ± 1.2	3.5 ± 0.9	.001
[a]6-Month remission, *n* (%)			
Yes	12 (87.5)	2 (12.5)	.014
No	25 (49.0)	26 (51.0)	
Number of AEDs (mean ± SD)	1.2 ± 0.4	1.4 ± 0.7	.169

TTT, time to treatment.
[a] *n* = 65.

treatment as the only independent predictor of lesser seizure severity (OR = 0.163, $p = .010$, 95% CI = 0.041–0.649). When 6-month disease remission was made the dependent variable, shorter time to AED treatment remained the only predictor of better 6-month seizure remission (OR = 0.154, $p = .023$, 95% CI = 0.031–0.770).

4. Discussion

Studies of the prognosis of epilepsy have identified basically three prognostic groups of individuals with epilepsy. These include 20–30% that will enter into long-term spontaneous remission, another 20–30% that will remain in remission only on AED and a third group (20–40%) that will continue to have recurrent seizures of varying frequencies and severities while on AED therapy with shared possibility of remission or refractoriness.[19] Our sample was made up of individuals who had epilepsy for prolonged periods of time and were not in long-term spontaneous remission before initiation of treatment.

Delayed initiation of treatment was a common phenomenon in our sample of people with epilepsy, in which only about a third initiated AED treatment for epilepsy in the first year of the disease, about a half within 5 years, and about a third after 10 years of epilepsy. This seems to confirm the fact that delayed identification and delayed treatment are the rule rather than the exception in resource-poor countries. Previous reports have consistently shown that the identification and treatment of epilepsy in resource-poor countries are often delayed, for various reasons, for as long as years or decades after the onset of the disease.[20,21] In a community-based study of AED treatment efficacy in rural Kenya, about 52% had epilepsy for more than 5 years without treatment[20] while in a similar study in rural Malawi, the mean duration of epilepsy before identification was 6.5 years.[21] Similar patterns have been reported from other developing countries such as Ecuador.[22] These stand in contradistinction to findings in Western Europe where reports uniformly indicate that most people with epilepsy receive treatment early. In a study of adolescents and adults (age 9–93 years) with epilepsy in Glasgow, Scotland, 56.4% of the subjects initiated treatment in less than a year of the onset of epilepsy, 85.8% within 5 years and only 6.5% after 10 years.[23] In another study of children and adults (age 3–84 years) with epilepsy in Bari and Monza in Italy, the mean disease duration before diagnosis was 35.5 months (range 0–66).[24] As the time individuals spend with epilepsy before initiation of treatment increases in a community, the epilepsy treatment gap of such community is expected to widen proportionately. Therefore, treatment gaps in most low-income countries exceed 75% while they are less than 10% in most high-income countries.[2] The wide treatment gaps found in resource-poor countries have been attributed to a wide range of potential factors and some of these factors may play a role in the long treatment delay found in our sample of patients though this was not a focus of our study. These factors include relatively high cost of seeking epilepsy treatment, inadequate skilled manpower, cost of treatment, and unavailability of drug, cultural beliefs, competing influence of ineffective traditional treatment, and distance to health facilities.[25]

The results of this study also suggest that delayed time to AED treatment is independently associated with increased seizure severity and decreased likelihood of disease remission following AED treatment. Time to AED treatment may be an important outcome predictor in high treatment gap settings. Our findings suggests that duration of epilepsy before the initiation of AED treatment may be more predictive of long-term disease outcome compared to other time-related variables such as the total duration of epilepsy, duration of treatment, or the age of onset of epilepsy. Studying the relationship between time to AED treatment and seizure

outcome in chronically untreated populations would be best done in a randomized trial, but such a study cannot be done for ethical reasons. However, there is substantial evidence from other sources that the risk of recurrence increases with increasing number of seizures in some groups of people with epilepsy. Mohanraj and Brodie in Glasgow found that quite often the number of seizures and not the duration of epilepsy before the initiation of treatment predicted seizure outcome after treatment was eventually commenced.[23] A similar finding was reported in the Bari and Monza (Italy) study in which the number of seizures and not the duration of epilepsy before treatment initiation predicted seizure outcome.[25] The subjects in these studies, however, are not comparable to ours as they had much shorter disease duration before treatment initiation. Circumstantial evidence from large epidemiologic studies of populations comparable to ours suggests that neither the total number of seizures before initiation of treatment nor the TTT predicts treatment outcome in individuals with long years of treatment delay.[20,21] This supports the view that early treatment does not necessarily account for the high remission rates seen in epilepsy. However, recent preclinical and clinical studies suggest that neuronal ultrastructural changes occur with large numbers of seizures occurring over long periods of time.[15] Loss of synaptic elements occurs in direct proportion to the total number of seizures in a life time and the distance of the brain area from the seizure focus.[26] Few reports from clinical sources have suggested that epilepsy duration before treatment initiation may predict outcome after treatment initiation. Abduljabbar et al. in a hospital-based study of adults with epilepsy in Saudi Arabia identified short epilepsy duration before treatment among other factors as an independent predictor of seizure control.[8] We did not assess the number of seizures before treatment initiation, so its effect on seizure outcome could not be determined in our study. This could be a pointer to the possibility of disease duration surrogating for number of seizures particularly in individuals with longstanding untreated active epilepsy.

Lastly, this study demonstrates that a treatment gap may exist between individuals with earlier age of onset of epilepsy and those with older age of onset of the disease. Those with earlier age of onset had a higher likelihood of initiating treatment after 5 years of the onset of the disease, while the reverse was the case for those with older age of onset. A similar pattern has been reported in large epidemiologic studies of mental health disorders. Individuals with younger age of onset were more likely to have no treatment contact and to have delayed treatment after the onset of mental disorders.[27,28] However, the relationship between age of onset and the duration of untreated epilepsy has not been the focus of past epilepsy studies.

Our study suggests that early age of onset of epilepsy may be disadvantaged as far as TTT initiation is concerned. While the dynamics and the factors responsible for delayed treatment in individual subjects were not the focus of this study, a possible explanation for this age-specific gap may include the high rate of misdiagnosis in childhood epilepsy.[29] Epilepsy is more likely to be misdiagnosed or undiagnosed altogether in resource-poor settings, where a large proportion of individuals with epilepsy do not have access to quality care.[2]

The assessment of seizure severity in this study was subjective and retrospective, besides, the subjects' profile of seizure frequency prior to the initiation of treatment was not explored. These limit the inferences that can be drawn from this study. Epilepsy is a highly heterogeneous disorder comprising of a wide range of syndromes and diseases of varying etiologies, courses, and prognoses. Magnetic resonance imaging and video-EEG could not be done, otherwise, these would have aided in profiling the characteristics of the different clinical groups.

5. Conclusions

The results of this study confirm the findings of past studies that delayed initiation of epilepsy treatment is the rule rather than the exception in resource-poor countries. This study also provides evidence that prolonged duration of untreated epilepsy independently predicts poor seizure outcome following eventual treatment initiation. This underscores the need for community-based interventions in high treatment gap communities that are targeted at optimizing the TTT initiation as this is key to outcome in epilepsy. Earlier onset of epilepsy may be disadvantaged with regard to early treatment initiation for epilepsy. Larger community-based, prospective studies in resource-poor settings are needed to confirm the findings of this study.

Conflicts of interest

All authors have none to declare.

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