Original Article

# Reported Incidence of Cluster Seizures in Persons with Epilepsy Experience from Two Tertiary Hospitals in Enugu South East Nigeria

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## Abstract

**Background:** Repetitive seizures are neurological emergencies which may occur in people with epilepsy. Ascertaining the incidence of these episodes of such seizures in the community is wrought with many challenges and few reports exist in sub Saharan Africa, a region with a high burden of epilepsy. The aim of this study was to describe the caregiver reported frequency of acute recurrent seizures in people with epilepsy attending neurology outpatient clinic in Enugu.

**Methods:** This cross-sectional study was performed in the medical out-patient clinics in Enugu Nigeria. Data were collected using a structured questionnaire from an existing epilepsy register. Cluster seizures were defined as frequent repetitive seizures (two or more) occurring more than usual within a week. Epilepsy was defined based on ILAE criteria.

**Results:** A total of 73(45.3%) reported a lifetime history of cluster seizures; similar in males 39(48.1%) and females 34(45.9%). P=0.73. About36.4% and 38.2% of PWE who had a history of traumatic brain injury and stroke had also experienced at least one SC. A large proportion of PWE with SC also had experienced status epilepticus in the past. Seizure cluster was correlated by older age of onset, having various forms of seizures and longer seizure freedom.

**Conclusions:** The reported lifetime history of cluster seizures among people with epilepsy attending a tertiary hospital clinic is high. This may suggest both poor seizure control and severity. Careful patient education will improve both adherence and emergency management of epilepsy to reduce the morbidity of epilepsy in the community.

**Keywords:** Repetitive seizures; Cluster seizures; Status epilepticus; Epilepsy; Nigeria.

## Introduction

Repetitive seizures are neurological emergencies (which may occur in people with epilepsy (PWE) as well as in those without epilepsy) and have been associated with high morbidity, mortality and low quality of life. Having such episodes of seizures have added clinical relevance in PWE[1,].Historically the definition of repetitive seizures (seizure clusters, cluster seizures, SC) is wrought with some controversy[3]. Currently there is no standard definition of a SC however in clinical trials, a common approach is to define SC as either ≥ 2 or ≥ 3 seizures in a 24-hour period[2,4]. A

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clinically useful definition is series of seizures closely grouped in time with shorter than normal inter ictal periods has been recommended[2]. Another common clinical approach is to consider clustering as an increase over the patient's typical seizure frequency[2]. Hence SC can be experienced over a time frame as short as several minutes to days[2,4].

Ascertaining the incidence and prevalence of SC in the community is wrought with many challenges[2] thus most available studies are hospital based. Thus, in population-based studies the prevalence of SC ranged widely in studies[2]. Major reason for this may be the lack of standard definition and difficulty associated with case ascertainment especially in non-convulsive seizures (NCS). Rates ranging from 13% to 76% have reported with hospital-based studies reporting higher rates[2]. A crude prevalence of 2.3 per 10,000 was reported in the UK[5]. A European study reported a 17.5% rate of SC over a 24-hour period[6]. Catamenial epilepsy (which may present as SC) has been described in up to 10-40% of women with epilepsy[7]. Most cases of documented SC are likely to be seizures with predominantly motor features hence non-motor types may be under reported.

Risk factors SC are reported to be similar to those of status epilepticus, because SC may progress to status epilepticus[4,8]. These risk factors include extra temporal seizure onset ( particularly frontal lobe onset), a history of head trauma with loss of consciousness; longer duration of epilepsy; history of status epilepticus; and poor seizure control[2,9] For patients with focal seizures, the strongest risk factor for SC appears to be a previous experience of clustering[9]. Considering the epidemiological characteristics of epilepsy in SSA, factors such as infections and non-adherence to medication are likely to be common causes. In Kenya, for example, documented risk factors for SE included neurologic impairments, acute encephalopathy, previous hospitalization, and presence of antibody titers to falciparum malaria and HIV[10]. These risk factors should be expected to be the same for SC.

The frequency of seizures including SC is a strong determinant of quality of life in PWE and their caregivers and also impacts on the economic burden of epilepsy[1,11,12]. With dearth of medical work forcein most SSA communities, PWE who have SC may be treated at home, by primary care physicians and even traditional healers. whichmay result in high morbidity and mortality. Despite the potential for poor outcomes ofSC in PWE, we are not aware of any research related to the subject in south east Nigeria. Recognizing frequency and patterns of these severe forms of seizures is helpful in preventing untoward consequences of SC. The aim of this study therefore, was to describe the caregiver or patient reported frequency and pattern of SC in PWE attending neurology outpatient clinic in Enugu. The aim of this study therefore, was to report the frequency and pattern of SC in PWE attending neurology outpatient clinic in Enugu.

## Methods

This cross-sectional study was performed in the medical out-patient clinics of the University of Nigeria Teaching Hospital Enugu and Enugu State Teaching Hospital. Data were collected using a structured questionnaire from epilepsy register of PWE attending the medical outpatient clinic of both hospitals. At the time of the study the register contained data from epilepsy patients attending adult neurology clinic of the Enugu state University Teaching Hospital. All patients gave their consent before recruitment into the data base. Questionnaire were filled out by the key investigator or research assistants. We excluded patients with possible psychogenic non-epileptic seizures, a single epileptic seizure, or those with developmental cognitive abnormalities. Cases of incomplete data or illegible data were excluded. Seizure cluster was defined as frequent repetitive seizures (two or more) occurring more than usual within a week. Epilepsy was defined based on ILAE criteria[13]. Ethical clearance was obtained from the ethics committee of the teaching Hospitals.

## Statistical Methods

The SPSS version 22 (IBM Corporation, New York, USA) was used for database management and statistical analysis. Data were presented in tables. The statistical methods included Mann-Whitney U test for unpaired observations and Chi-squared test for comparison of categorical data. The frequency of SC was calculated as the percentage of participants. Mean and median were calculated and values were

presented as tables. In all, $p < 0.05$ was regarded as statistically significant. Conclusions were drawn at this level of significance at 95% confidence level.

## Results

Data of 154 PWE were reviewed and analysed. Males were 80(51.9%) and females were 74(48.1%) were females. The male to female ratio was 1:1.1. Most participants were aged 20-29 years (42.9%) with a mean age of 32.4(17.3) years. Males were older than females by almost 7 years. P<0.01. other characteristics of the patients are shown in Table 1. Before presenting to the hospital 40(26%) used traditional herbal drugs while 36(23.4%) resorted to prayer as a sole means of treatment.

## Seizure characteristics

Reported seizures characteristics are shown in table 2. The mean age of onset of epilepsy in the cohort was 20.9 years (with a median of 17 years); earlier in females (14.4 years) than males 26.3 years). P <0.01. The peak age of onset of epilepsy in SC was 0 to 9 years. The mean time taken from the age of onset to the age of going to the hospital was similar in both males and females. P=0.2. The 6-month seizure freedom was 9.7%. More males reported a family history of epilepsy. P=0.03. About 45.5% reported a clinical history of generalized seizures. Among those that had focal seizures clinically, 38(45.2%) could always predict the onset of seizures while the rest did so sometimes. Clinically seizures were reported to be similar every time by 107(69.5%).

Figures 1 and 2 shows the peak ages of onset of repetitive seizures and prolonged seizures.

A total of 73(45.3%) of all adult cases presenting within the period of the study confirmed that they had experienced SC in the past; this was similar in males (39(48.1) and females 34(45.9%). P=0.73. Seizure related admissions were reported in 14(9.1%) PWE more in females 11(14.9%) than males 3(3.8%).See Table 2.

Table3 shows the proportion of PWE with various risk factors who had SC. About 38.2% of PWE who had traumatic brain injury and 36.4% of stroke cases experienced SC. All dementia cases also had SC although the overall numbers were few. This is the same for those with meningitis and migraine. Furthermore, a large proportion of PWE with a history of status epilepticus in the past also had experienced repetitive seizures. History of SC correlated older age of onset, having various forms of seizures and longer seizure freedom.

**Table 1:** Age and gender distribution of the Patients

| Gender | Male (%) | Female (%) | Total (%) | p-value |
|---|---|---|---|---|
| N (%) | 80(51.9) | 74(48.1) | 154(100) | 0.63 |
| **Age (years)** | | | | |
| **Mean age (sd)** | 35.8(18.9) | 28.7(14.5) | 32.4(17.3) | 0.01 |
| **Median age** | 29.5 | 28.7 | 26 | |
| **Age group** | | | | |
| < 20 | 11(13.8) | 14(18.9) | 25(16.2) | |
| 20-29 | 29(36.3) | 37(50) | 66(42.9) | |
| 30-39 | 15(18.8) | 13(17.6) | 28(18.2) | |
| 40-49 | 8(10) | 3(4.1) | 11(7.1) | |
| | 17(21.3) | 7(9.5) | 24(15.6) | 0.1 |
| **Level of education** | | | | |
| No education | 15(18.8) | 4(5.4) | 19(12.3) | |
| Primary | 13(16.3) | 9(12.2) | 22(14.3) | |
| Junior secondary | 6(7.5) | 14(18.9) | 20(13) | |
| Senior secondary | 30(40.7) | 32(43.2) | 62(40.3) | |
| Tertiary | 16(20) | 15(20.3) | 31(20.1) | 0.04 |
| **Occupation** | | | | |
| Students | 17(21.3) | 28(37.8) | 45(29.2) | |
| Employed | 37(46.3) | 31(41.9) | 68(44.2) | |
| Unemployed | 17(21.3) | 13(17.6) | 30(19.5) | |
| Retired | 9(11.3) | 2(2.7) | 11(7.1) | 0.05 |
| **Substance use** | | | | |
| Alcohol use | 22(27.5) | 6(8.1) | 28(18.2) | <0.01 |
| Tobacco | 11(13.8%) | 3(4.1) | 14(9.1) | 0.04 |
| Marijuana | 5(6.3) | - | 5(3.2) | 0.03 |
| Glue | - | 1(1.4) | 1(0.6) | 0.3 |
| **Alternative treatment** | | | | |
| Herbal | 25(31.3) | 15(20.3) | 40(26) | 0.12 |
| Prayer house | 16(20) | 20(27) | 36(23.4) | 0.3 |
| Drug store | 7(8.8) | 3(4.1) | 10(6.5) | 0.24 |

**Table 2:** Gender distribution of seizure characteristics

| Gender | Male (%) | Female (%) | Total (%) | p-value |
|---|---|---|---|---|
| **Age of onset** | | | | |
| Mean age (sd) | 26.3(21.7) | 14.4(14.9) | 20.9(15.3) | <0.01 |
| Median age | 18 | 12 | 17 | |
| **Time taken before first hospital visit (years)** | | | | |
| Mean age (sd) | 1.6(4.5) | 2.7(5.3) | 2.1(0.4) | 0.2 |
| Median (range) | 0(0-28) | 0(0-21) | 0(0-28) | |
| **Last seizure episode** | | | | |
| < 24 hours | 18(22.5) | 20(27) | 38(24.7) | |
| 1-7 days | 18(22.5) | 16(21.6) | 34(22.1) | |
| 1-4 weeks | 16(20) | 12(16.2) | 28(18.2) | |
| 1-6 months | 21(26.3) | 18(24.3) | 39(25.3) | |
| >6 months | 7(8.8) | 8(10.8) | 15(9.7) | 0.97 |
| **Family History** | 16(19.8) | 5(7.2) | 21(14) | 0.03 |
| ***Prediction of seizures*** | | | | |
| Always | 21(26.3) | 17(23) | 38(24.7) | |
| Sometimes | 17(21.3) | 29(39.2) | 46(29.9) | |
| Never | 42(52.5) | 28(37.8) | 70(45.5) | 0.05 |
| **Seizures are similar** | 54(67.5) | 53(71.6) | 107(69.5) | 0.58 |
| History of Seizure Clusters | 39(48.8) | 34(45.9) | 73(45.3) | 0.73 |
| Seizure related admissions | 3(3.8) | 11(14.9) | 14(9.1) | 0.02* |
| Total | 80(51.9) | 74(48.1) | 154(100) | |

*Mann-Whitney U Test.

**Table 3:** Distribution of seizure clusters by various documented risk factors

| Risk factor | N(%) | Cluster# |
|---|---|---|
| No risk factor | 84(54.5) | 41(48.8) |
| Status epilepticus | 56(36.4) | 35(62.5) |
| Traumatic brain injury | 34(22.1) | 13(38.2) |
| Stroke | 11(7.1) | 4(36.4) |
| Alcohol abuse | 5(1.9) | 3(60) |
| Mental retardation | 4(1.9) | - |
| Dementia | 4(2.6) | 4(100) |
| Meningitis | 3(1.3) | 2(66.7) |
| Migraine | 3(1.9) | 2(66.7) |
| AIDS | 3(0.6) | - |
| Brain surgery | 2(2.6) | 1(50) |
| ___ | 1(3.2) | - |
| Psychosis | 1(0.6) | - |
| Hypertension | 20(13.3) | 6(30) |
| Diabetes | 5(3.2) | - |
| Heart failure | 1(0.6) | - |
| Total | 154* | 75(45.3) |

*Multiple risk factor was recorded.
#Percentage of risk factors.

**Table 4:** Correlates of Status epilepticus and Seizure clusters

| Gender | Seizure Cluster r (p-value) |
|---|---|
| Status epilepticus | 23(<0.01) |
| Age | 0.14(0.87) |
| Gender (1 male, 2 female) | 0.03(0.73) |
| Family history | 0.12(0.15) |
| Age of onset of epilepsy | **0.31(<0.01)** |
| Seizure type (1 generalized, 0 focal) | -0.05(0.56) |
| History injuries (1 yes, 2 No) | -0.13(0.11) |
| Seizure related admissions (1 yes, 0 No) | 0.12(0.19) |
| First point of care (0 hospital, 1 other places) | -0.13(0.11) |
| Seizures semiology (1 similar, 0 varies) | **-0.19(0.02)** |
| Last seizure (1 less than 24 hours to 6 greater than 6 months) | **-0.31(<0.01)** |

## Discussion

The frequency and pattern of seizures to a great extent determine the burden of epilepsy. Although in PWE, seizures are generally sporadic or even infrequent[7], however they may experience SC. Identification of SC is very important because of the associated high morbidity, mortality as well as the associated high direct and indirect health costs in epilepsy[11,12]. In the index study, the male to female ratio of PWE with a history of SC was 0.9:1. A total of 73(45.3%) confirmed that they had experienced SC in a day or within few days; similar in males (39(48.1) and females 34(45.9%). P=0.73).

About 36.4% of those with a past medical history of stroke reported SC. Furthermore, a large proportion of PWE with status epilepticus also had experienced status epilepticus in the past. SC was correlated by older age of onset, having various forms of seizures and longer seizure freedom.

The epilepsy related characteristics in the index study is similar to published works from Nigeria[14,15]. The age distribution of the patients in the index study may suggest a changing pattern of epilepsy risk factor or increasing awareness of epilepsy in the country. Younger mean-age-of-onset in females may be attributed to a better health seeking behaviour among females. However, there latively large proportion of individuals with hypertension, diabetes and stroke may be contributory. These disorders are generally commoner in older males. Clinically, 54.5% had focal seizures, a finding which may be explained by the high rates of risk factors for focal seizures in the study. This is similar to previous studies[16]. Six-month seizure freedom in the index study was a mere 9.7% while 24.7% reported within 24 hours of seizures. These findings support previous reports on seizure control in PWE in Nigeria[23]. These may be related to several factors including non-adherence, use of unorthodox medicine and alcohol[15,] Treatment seeking behaviour of PWE may also be a factor as some PWE may come to hospitals after they have experienced seizures.

Current populations demographics in Nigeria and SSA have shown a rise in the older age group; therefore, SC is likely to become a common problem and an important health issue in years to come.

There are no community-based studies on SC from Nigeria. Community based studies are usually based on recall of previous events which may be limited by the ability of onlookers to recognize a seizure-types and record their duration appropriately. Even in hospital settings in SSA, EEG monitory in the ICU may not be done in every patient. The evolution of the definition of SC, the incidence/prevalence of SC conditions may not differ much.

The incidence of SC is related to the premorbid state of the patients[17,18]. In fact, metabolic disorders such as hyperglycemia are common causes of SC in non-epilepsy patients. The reported prevalence of SC in the index study is 45.3%. This value may be affected

by selection bias because tertiary centres such as ours may have an over representation of severe epilepsies and refractory epilepsies. Other factors such as methods of data collection and use of seizure diaries may also affect the prevalence of SC[2]. Our finding is within the reported prevalence in the literature (13% to 76% among out-patients and 18% to 61% among in patients)[12] . In a population-based UK study[5], the estimated crude prevalence of SC were 2.3 per 10,000 with an age-adjusted prevalence to be 2.5/10,000. In another Europe wide [6]study the prevalence of acute repetitive seizures was 17.5%. SC may be higher in young women because of catamenial epilepsy, in people with structural brain lesion and with non-adherence[2] to anti seizure medications.

Similar factors tend to precipitate and cause SE and SC hence PWE with epilepsy are at risk of having one if they have the other. A specific risk factor for SC recorded in the literature is seizure focus and a previous history of clustering[18]. SC is frequently associated with extra temporal foci especially frontal lobe focus. Other risk factors include traumatic brain injury, history of status epilepticus, longer duration of epilepsy and poor seizure control[19] In a study that used digital seizure diary[5], 28% of SC were related to sleep, 12% to mood/stress, 4% to menstrual periods, 4% to missed medication or medication changes, 3% to medical illness; and 1% to use of alcohol or recreational drugs.

SC has a direct effect on mortality, quality of life and increased health cost[12]. SC is also associated with postictal psychosis and to repeated admissions in the emergency room or even ICU[20,21]. Three factors that were correlated with SC to in the index study were age on onset of epilepsy, having identical seizure semiology and increasing duration of seizure freedom. Older age of onset may be explained by the proportion of stroke and TBI in the cohort. Since most of the cases in this study were reported by care givers, it is obvious only easily identifiable cases will be reported and this is most likely to be in those with similar seizure semiology. Shorter periods of seizure freedom also correlated with SC, suggesting that it may be reason for patient's eventual presentation. Non-adherence to AEDs has been related to Sc[10].

SC is a condition for which data on incidence, etiology, risk factors and outcomes are required for proper decision-making and for the allocation of resources by policy makers. These resources need to be used in the development of strategies that help improve prevention, diagnosis and reduce morbidity and mortality.

## Limitations

This study has some limitations. Firstly, PWE and their caregivers were required to recall past episodes of SC. This may affect the true prevalence because of recall bias. In addition to this only predominately motor seizures will be observed and subtle form of seizure are likely to be overlooked. Secondly, the study addressed only survivors, mortality rates of SC are important in assessing the true burden of these complications of epilepsy. Lastly, case definition of SC of recurrent seizures with a week may overestimate the actual prevalence of SC. Cases of catamenial seizures were also not identified. Furthermore, studied that depend on recall of previous events such as this are usually based on recall of previous events may be limited by the ability of onlookers to record the duration of the ictus These limitations notwithstanding, this study has provided data for comparison for future studies. Large multi-center and community-based studies are needed to accurately document the prevalence of SC in Nigeria.

## Conclusion

The reported lifetime history of SC in PWE attending a tertiary hospital clinic is high. This may suggest both poor seizure control and severity. Careful patient education will improve both adherence and emergency management of epilepsy to reduce the morbidity of epilepsy in the community.

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