

Factors predisposing patients with temporal lobe epilepsy to seizure cluster

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Keywords

Seizure; Electroencephalography; Neurologic Manifestations; Magnetic Resonance Imaging

Abstract

Background: We aimed to identify the potential risk factors associated with seizure clusters in patients with temporal lobe epilepsy (TLE).

Methods: This retrospective cross-sectional study was performed on all the consecutive patients with TLE, who were admitted to the Epilepsy Monitoring Unit (EMU), Loghman-Hakim Hospital, Tehran, Iran. Seizure cluster was defined as three or more habitual seizures occurring within 24 hours, in over 50% of ictal events, with inter-seizure interval of less than 8 hours. The patients' demographic data, epilepsy duration, seizure frequency, frequency of interictal epileptiform discharges (IEDs), and brain magnetic resonance imaging (MRI) findings were collected.

Results: Among a total number of 124 patients with TLE, 62 (50.0%) patients reported seizure clusters. In addition, 44 (37.9%), 42 (36.2%), and 30 (25.9%) patients had normal-appearing brain MRI, mesial

temporal sclerosis (MTS), and other brain pathologies, respectively. In terms of IEDs frequency, 35 (29.4%), 43 (36.1%), 17 (14.3%), and 24 (20.2%) patients had respectively frequent, occasional, rare, and no spikes in one-hour of interictal scalp electroencephalography (EEG) recording. In our study, seizure clusters were not associated with the epilepsy duration ($P = 0.100$), the amount of IEDs ($P = 0.764$), or MRI findings ($P = 0.112$).

Conclusion: In patients with TLE, seizure clustering had no correlation with the epilepsy duration, the amount of IEDs, or brain MRI findings.

Introduction

Among roughly 1-2% of the general population who suffer from epilepsy, one-third are drug-resistant.¹ A subgroup of patients with drug-resistant epilepsy have seizure clusters, also known as acute repetitive seizures.²

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Seizure cluster is not listed in the International League Against Epilepsy (ILAE) commission on classification and terminology.³ Different terminologies have been used to describe this clinical entity: “acute repetitive seizures”, “flurries”, “cyclical, serial, repetitive, crescendo, and recurrent seizures”.⁴ Basically, “seizure cluster” refers to a set of closely grouped seizures.^{5,6} However, the number of seizures and the period of inter-seizure-interval (ISI), are subject of controversy. One proposed clinical definition is three or more seizures within 24 hours, with average ISI of less than 8 hours.⁷

Two recent studies have decreased both the number of seizures and ISI required to define “seizure cluster” to more than 2 seizures occurring within 6 hours.^{8,9}

The prevalence of seizure cluster varies significantly in different studies depending on the definitions used and the study population, reporting between 13 to 76% in the outpatient and 18 to 83% in the inpatient setting [epilepsy monitoring unit (EMU)].^{4,10-14} Given the previous studies, patients with extratemporal epilepsy, especially frontal lobe epilepsy (FLE), are more prone to seizure clusters and clustering is considered to be one of the characteristics of FLE.^{5,10,15} However, temporal lobe epilepsy (TLE), especially mesial temporal sclerosis (MTS) has been shown to be associated with seizure clusters.¹⁶

Clusters have a negative impact on the quality of life (QOL) and associated with a wide range of complications and if not managed appropriately, may evolve into status epilepticus (SE).^{5,10,17} The etiology of seizure clusters is poorly understood; however, the basic mechanism is assumed to be the failure of termination of the excitable seizure focus or increased excitation of neuronal circuits that cause epilepsy.^{17,18} Most of the previous studies on seizure clusters focused mainly on the abortive medications, rather than conditions that predispose certain patients susceptible to clusters.

The aim of this study was to determine the factors associated with increased risk of seizure clusters in patients with temporal lobe epilepsy (TLE). The study population was selected from patients with TLE because seizure clusters are common in FLE and is somehow considered as a characteristic feature of this type of epilepsy. We sought to determine if epilepsy duration, frequency of interictal epileptiform discharges (IEDs), and brain magnetic resonance imaging (MRI) findings have played a role in clustering.

Materials and Methods

In this retrospective study, all the consecutive patients who were diagnosed with drug resistant TLE and admitted to the EMU of Loghman-Hakim Hospital, Tehran, Iran, between 2016 and 2020 were recruited. The diagnosis of epilepsy type was made by trained epileptologists, based on the patients' history, the ictal and interictal electroencephalography (EEG) findings, and the seizure semiology. Patients suspected to other types of epilepsy were excluded from the study. According to the ILAE definition, drug resistant epilepsy is defined as failure of adequate trials of two tolerated and appropriately chosen and used anti-seizure medications (ASMs) (whether as monotherapies or in combination) to achieve sustained seizure freedom.

The patients' demographic data (age, sex), age at epilepsy onset, epilepsy duration, and seizure types and frequency were collected. The duration of patients' EMU admission depended mainly on the time needed to capture enough habitual ictal events, as well as, the patients' financial condition to cover the hospital expenses. The duration range of EMU admission was between 48 hours to 5 days. The frequency of IEDs was determined for each patient and expressed in four categories of none, rare, occasional, and frequent, with rare, occasional, and frequent spikes including those with one spike, 2-60 spikes, and more than 60 spikes in one hour of scalp EEG recording, respectively.¹⁹ The frequency of IEDs was measured manually in one hour of EEG epochs [recording in the international 10-20 system/low frequency filters (LFF): 1Hz, high frequency filters (HFF): 70 Hz) during drowsiness and/or non-rapid eye movement (NREM) sleep, with the minimum amount of EEG artifacts]. Suspicious findings were discussed with other experts and reported based on the experts' consensus. To reduce the effect of tapering ASMs on IEDs frequency, IEDs were measured in the first day of EMU admission, before occurring ictal events, while the serum ASMs levels were still in the therapeutic range.

For all the patients recruited, 1.5 tesla brain MRI with standard epilepsy protocol was performed and reported by an expert neuroradiologist.

The patients were divided into two groups of positive (cluster+) and negative (cluster-) seizure clusters. The seizure cluster was defined as having three or more habitual ictal events within 24 hours, in at least 50% of episodes, with ISI of less than 8 hours and the seizure frequency was determined

based on the patients' seizure diary. Patients with high seizure burden frequency, e.g. daily or weekly attacks, were not considered as clusters+ and were excluded from the study. Patients were considered as having seizure clusters only if they routinely experienced seizure-free intervals of at least 2 weeks between clusters.

The Statistical Package for the Social Sciences (SPSS) software (version 22, IBM Corporation, Armonk, NY, USA) was applied for data analysis. Kolmogorov-Smirnov test was used to assess the normal distribution of variables. The numeric and categorical variables were expressed as mean \pm standard deviation (SD), frequency, and percentage, respectively. The independent sample t-test and chi-square test were performed to analyze the differences between the two groups in terms of quantitative and categorical data. The results were expressed as 95% of confidence intervals (CIs), and P value < 0.050 was considered statistically significant in all tests.

Results

In this retrospective cross-sectional study, 124 patients with diagnosis of TLE were enrolled

(including 50% female and 50% male with the mean age of 31.97 ± 10.52 years). Based on the video-EEG monitoring findings, 49 (39.8%), 71 (35.7%), and 3 (2.4%) patients had right TLE, left TLE, and bilateral TLE, respectively. The mean epilepsy duration was 14.96 ± 8.64 years and the mean seizure frequency was 17.20 ± 84.12 attacks per month.

Among 124 patients, 62 (50.0%) patients had a history of cluster seizures and the other 62 (50.0%) lacked seizure clusters. In terms of brain MRI findings, 44 (37.9%) patients had normal-appearing brain MRI scan, 42 (36.2%) had MTS, and 30 (25.9%) had other brain pathologies including vascular malformations, malformations of cortical development, gliosis, or non-specific findings. In terms of IEDs frequency, 35 (29.4%), 43 (36.1%), 17 (14.3%), and 24 (20.2%) patients had respectively frequent, occasional, rare, and no spikes in one-hour of interictal scalp EEG recording.

There were no significant differences in terms of demographic characteristics between the two groups ($P > 0.050$). The clinical features of the patients are presented in table 1.

Table 1. Demographic and clinical data of the study groups

Variables	Total TLE (n = 124)	Positive cluster (n = 62)	Negative cluster (n = 62)	P
Sex [n (%)]				
Male/Female	62 (50)/62 (50)	32 (51.6)/30 (48.4)	30 (48.4)/32 (51.6)	0.719
Age (year)	31.97 ± 10.52	33.51 ± 9.93	30.43 ± 10.93	0.100
Epilepsy duration (year)	14.96 ± 8.64	16.22 ± 8.81	13.72 ± 8.35	0.100
Focal seizure frequency (per month)	17.20 ± 84.12	10.64 ± 13.56	23.22 ± 115.87	0.426
GTCs in the past 2 years				
Yes	47 (38.5)	23 (38.3)	24 (38.7)	0.966
No	75 (61.5)	37 (61.7)	38 (61.3)	
Febrile convulsion				
Yes	31 (26.1)	14 (23.7)	17 (28.3)	0.567
No	88 (73.9)	45 (76.3)	43 (71.1)	
Epilepsy lateralization				
Right	49 (39.8)	23 (37.7)	26 (41.9)	0.203
Left	71 (35.7)	35 (57.4)	36 (58.1)	
Bilateral	3 (2.4)	3 (4.9)	-	
IEDs frequency				
None	24 (20.2)	11 (18.1)	13 (22)	0.764
Rare	17 (14.3)	10 (16.7)	7 (11.9)	
Occasional	43 (36.1)	20 (33.3)	23 (39)	
Frequent	35 (29.4)	19 (31.7)	16 (27.1)	
MRI findings				
Normal	44 (37.9)	17 (29.8)	17 (45.8)	0.112
MTS	42 (36.2)	21 (36.8)	21 (35.6)	
Others	30 (25.9)	19 (33.3)	11 (18.6)	

Data are presented as mean \pm standard deviation (SD) or n (%).

TLE: Temporal lobe epilepsy; GTC: Generalized tonic-clonic seizures; IEDs: Interictal epileptiform discharges; MRI: Magnetic resonance imaging; MTS: Mesial temporal sclerosis

In addition, there were no differences in terms of the amount of IEDs, epilepsy duration, seizure frequency, and brain MRI findings between the two study groups ($P > 0.050$).

Discussion

Seizure cluster could be considered as a sign of upcoming SE needing urgent abortive medications known as "rescue medicine". It has negative impacts on patients' QOL, emotional wellbeing, and daily functions and could result in increased seizure-related hospitalization.^{20,21} Patients with a history of seizure clusters have a 2.5-fold increased risk of sudden unexpected death in epilepsy.²² Seizure clusters and SE have shared underlying pathophysiological mechanisms including failure of brain's inhibitory self-regulatory mechanisms or persistent lowering of seizure threshold.^{18,21}

In a study by Ferastraoaru et al., it was found that in comparison to isolated seizures, the initial seizures of a cluster are too brief to activate inhibitory mechanisms, while the last seizure is prolonged enough to activate inhibitory mechanisms terminating a cluster.²¹ A recently published study indicated that focal, non-convulsive seizures at the beginning of a cluster enhance seizure progression and aggravate the seizure activity. However, the subsequent occurrence of a prolonged convulsive seizures shift the dynamics towards cluster termination.²³ Understanding the factors predisposing the individual to seizure clusters may help clinicians to better identify patients at risk. In our study, we did not find any specific correlation between the seizure clusters in patients with TLE with the epilepsy duration, seizure frequency, brain MRI findings, and even the frequency of IEDs.

Some previous studies focused on identifying the risk factors that predispose the patients to seizure clusters. Different triggers have been described, such as sleep deprivation, stress, fever or illness, missing or changing medications, alcohol, and menstruation.^{6,14,16} However, seizure clusters may occur in the absence of any identified trigger. Moreover, some patients never experience seizure clusters even in the presence of multiple triggers. In catamenial epilepsy, an example of seizure cluster, the seizure susceptibility is driven by hormonal plasma level alterations.²⁴ As a result, it may presume that an endogenous vulnerability, like a circuit of damaged neuronal network, predisposes certain patients to develop seizure clusters.

In our study, we investigated the possible role of

IED frequency on occurring seizure clusters. There are contradictory reports regarding the association between the neural network that generates IEDs and the network that produces seizures. Several studies are in favor of the correlation between higher amount of IEDs with higher probability of occurring seizures.²⁵⁻²⁹ Nevertheless, another theory believes that IEDs may inhibit rather than generate seizures.³⁰ In our study, we did not find any correlation between the amount of IEDs and the occurrence of seizure clusters.

Based on several studies, patients with extratemporal epilepsies, especially FLE, are more susceptible to seizure clusters.^{5,10} However, TLE, especially MTS, has also been shown to be associated with seizure clusters.^{16,21,31} Ferastraoaru et al. reported that among localization-related epilepsies, temporal and frontal epilepsy are more associated with seizure clustering.²¹ Moreover, recent head trauma was reported to be associated with clusters, irrespective of the type of epilepsy.¹⁰ In our study, no association was found between a specific brain MRI finding and occurrence of seizure clusters. In line with our finding, a previous study performed on a heterogeneous group of patients with epilepsy did not find any association between a specific brain MRI finding and clustering.¹⁷

Another factor investigated in our study was the potential effect of seizure frequency and epilepsy duration on clustering. One previous study found that higher frequency of seizures has been significantly associated with the development of clusters.¹¹ The association reported between epilepsy duration and clustering was controversial. A study found that epilepsies with longer duration have the higher probability of developing clusters,³² while another study did not conclude this association.¹⁰ We did not find any association between seizure frequency or epilepsy duration with clustering. The most significant risk factor for seizure clusters is intractable epilepsy.^{10,33} Both of our study groups were selected from drug-resistant patients with TLE.

The present study had some limitations including the limited sample size and relying on the patients' history and seizure diary. Moreover, the present study groups were selected from patients with TLE and it is suggested that a study be conducted on a larger group of patients with different epilepsy types.

Conclusion

Our study did not show any significant correlation

between seizure clustering with the epilepsy duration, seizure frequency, the amount of IEDs, and brain MRI findings in patients with drug resistant TLE.

Conflict of Interests

The authors declare no conflict of interest in this study.

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