Epilepsy Research 133 (2017) 98–102

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Prevalence and risk factors of seizure clusters in adult patients with epilepsy

Baibing Chen[a,*], Hyunmi Choi[b], Lawrence J. Hirsch[a], Austen Katz[a], Alexander Legge[b], Rebecca A. Wong[a], Alfred Jiang[a], Kenneth Kato[b], Richard Buchsbaum[b], Kamil Detyniecki[a]

[a] Comprehensive Epilepsy Center, Dept. of Neurology, Yale University, New Haven, CT, United States
[b] Comprehensive Epilepsy Center, Dept. of Neurology, Columbia University, New York, NY, United States

ARTICLE INFO

Keywords:
Predictors
Risk factors
Intractable epilepsy
Benzodiazepine
Status epilepticus
Symptomatic generalized epilepsy
Seizure freedom
Lobe localization

ABSTRACT

Purpose: In the current study, we explored the prevalence of physician-confirmed seizure clusters. We also investigated potential clinical factors associated with the occurrence of seizure clusters overall and by epilepsy type.

Methods: We reviewed medical records of 4116 adult (≥16 years old) outpatients with epilepsy at our centers for documentation of seizure clusters. Variables including patient demographics, epilepsy details, medical and psychiatric history, AED history, and epilepsy risk factors were then tested against history of seizure clusters. Patients were then divided into focal epilepsy, idiopathic generalized epilepsy (IGE), or symptomatic generalized epilepsy (SGE), and the same analysis was run.

Results: Overall, seizure clusters were independently associated with earlier age of seizure onset, symptomatic generalized epilepsy (SGE), central nervous system (CNS) infection, cortical dysplasia, status epilepticus, absence of 1-year seizure freedom, and having failed 2 or more AEDs ($P < 0.0026$). Patients with SGE (27.1%) were more likely to develop seizure clusters than patients with focal epilepsy (16.3%) and IGE (7.4%; all $P < 0.001$). Analysis by epilepsy type showed that absence of 1-year seizure freedom since starting treatment at one of our centers was associated with seizure clustering in patients across all 3 epilepsy types. In patients with SGE, clusters were associated with perinatal/congenital brain injury. In patients with focal epilepsy, clusters were associated with younger age of seizure onset, complex partial seizures, cortical dysplasia, status epilepticus, CNS infection, and having failed 2 or more AEDs. In patients with IGE, clusters were associated with presence of an aura. Only 43.5% of patients with seizure clusters were prescribed rescue medications.

Conclusion: Patients with intractable epilepsy are at a higher risk of developing seizure clusters. Factors such as having SGE, CNS infection, cortical dysplasia, status epilepticus or an early seizure onset, can also independently increase one's chance of having seizure clusters.

1. Introduction

A clinically significant proportion of patients with epilepsy experience seizure cluster (Haut et al., 2005a, 2005b; Sinha et al., 2013; Haut, 2015). It has been challenging to accurately estimate the prevalence of seizure clustering. The lack of a precise definition of seizure cluster might be one of the main factors contributing to this challenge. Various specific definitions of seizure clusters have been used in past literature, including 3 seizure in 24 h (Haut et al., 2002; Yen et al., 2001), 2–4 seizures in less than 48 h (Caraballo et al., 2004), or 2 tonic-clonic seizures or 3 complex partial seizures in 4 h (Rose et al., 2003). Investigators have also proposed nonspecific definitions of seizure cluster, such as threefold to fourfold increase over patient's usual seizure frequency (Haut, 2006), or multiple seizures with distinguishable pattern from patient's usual seizure pattern occurring within 24 h for adults or within 12 h for children (Dreifuss et al., 1998).

There might also be a general overestimation of seizure cluster prevalence since many of the published literature collected data from tertiary epilepsy centers with large populations of patients with refractory epilepsy. Estimates of seizure cluster prevalence are inconsistent in populations of patients with epilepsy, ranging from 3% to 57% in outpatient studies (Haut et al., 2005a; Haut, 2015; Milton et al., 1987; Bauer and Burr, 2001; Tauboll et al., 1991; Martinez et al., 2009).

Preliminary studies have reported risk factors that include extra temporal lobe epilepsy, particularly frontal lobe epilepsy, head trauma, status epilepticus, refractory epilepsy and poor seizure control, and increased duration of epilepsy (Haut et al., 2005a; Sinha et al., 2013; Haut, 2015). Certain behavioral-related activities, including changes in

* Corresponding author at: Yale Comprehensive Epilepsy Center, 15 York Street, LCI 7, New Haven, CT 06520, United States.
E-mail address: baibing.chen@aya.yale.edu (B. Chen).

http://dx.doi.org/10.1016/j.eplepsyres.2017.04.016
Received 19 October 2016; Received in revised form 17 April 2017; Accepted 22 April 2017
Available online 27 April 2017
0920-1211/

sleep, stress, and medication changes or non-compliance, can also heighten individual vulnerability to seizure clusters (Haut et al., 2005b).

Epilepsy patients with untreated seizure clusters experience significantly diminished quality-of-life and greater risks of status epilepticus, emergency room and hospital admissions, and increased morbidity and mortality, compared to non-clustering epilepsy patients (Haut, 2015; Kriel et al., 1991; Shafer, 1999; Balestrini et al., 2013). The personal health impacts of clustering and the confirmed efficacy and tolerability of rescue benzodiazepines (Haut, 2015; Kriel et al., 1991) provide justification for having an early rescue medication plan. There are few data that explore how many epilepsy patients, with or without seizure clusters, have a rescue medication plan. Currently, rectal diazepam is the only FDA approved medication for clustering. However, rectal delivery presents logistical and personal preference barriers to quick and easy administration. Intramuscular, buccal, sublingual, and intranasal rescue benzodiazepines are excellent options for at home seizure cluster treatment, offering equal to superior effectiveness, delivery and onset time, safety, and bioavailability compared to the current FDA approved standard (Haut, 2015).

In sum, there is a lack of large-scale studies that examine potential risk factors for clustering on the basis of epilepsy type, as well as frequency of rescue medication prescribed to patients who have seizure clusters. In the current study, we explored the prevalence of physician-confirmed clustering and the use of rescue benzodiazepines, and identified potential clinical factors associated with the occurrence of seizure clusters overall and by epilepsy type.

2. Methods

As part of the Columbia/Yale Antiepileptic Drug (AED) Database Project, we retrospectively reviewed medical records of 4116 adult (≥16 years old) outpatients with epilepsy, seen from January 1st, 2005 to December 31st, 2015 and were treated and followed up for at least 1 year at our centers. We reviewed all patient medical records available at our centers for documentation of seizure clusters. A patient was considered to have had a seizure cluster when 1) the patient self-reported at least 3 seizures in a 24-h period (or 3 times the daily average for patients with daily seizures) since starting treatment at one of our centers, and/or 2) there was closely grouped series of seizures, which was noted and identified as a seizure cluster by the patient's treating epileptologist at our centers. If a patient was identified as having had a seizure cluster(s) in his/her medical record, a box in the AED database was checked.

To investigate potential associations with overall seizure clustering, we first examined 86 different variables including patient demographics, epilepsy details, age of seizure onset (divided into age groups with 10-year intervals: 0–10, > 10–20, > 20–30, > 30–40, > 40–50, > 50–60, and > 60), medical and psychiatric history, AED history, various epilepsy risk factors (Supplementary Table 1). We then divided up the patients based on epilepsy type (focal/partial, idiopathic generalized, and symptomatic generalized) and ran the same analysis for each group. We also evaluated for any association between benzodiazepine rescue medication use and seizure clusters. Finally, we looked at the frequency of different benzodiazepine rescue medication prescription in the overall sample as well as by epilepsy type.

2.1. Statistical

We used logistic regression to test the correlation between each individual variable and the occurrence of seizure clustering. Variables that were significant in the univariate analysis ($P < 0.05$) were entered into a multivariable analysis where the significance level was adjusted using the Bonferroni method: $P < 0.05$/number of variables entered. Variables with a p-value between the Bonferroni-adjusted p-value and 0.05 were considered a trend.

3. Results

In our study, 55% of the patients were female. 69.9% of the study population identified as Caucasian, 13.4% identified as Hispanic, 9.8% identified as African American, 4.9% identified as Asian/Pacific Islander, 0.6% identified as American Indian/Alaskan Native, and 1.3% identified as other.

Overall, 14.9% (612/4116) of the patients had documentation of at least one seizure cluster. 16.3% of the patients with focal epilepsy, 7.4% with idiopathic generalized epilepsy (IGE; also known as genetic generalized epilepsy (Berg and Scheffer, 2011)), and 27.1% with symptomatic generalized epilepsy (SGE; also known as structural-metabolic epilepsy (Berg and Scheffer, 2011)) had documented seizure clusters. Patients who had seizure cluster(s) were significantly less likely to achieve 1-year seizure freedom (27.8%; 170/612) compared to patients who never had seizure clusters (50.9%; 1783/3504; $P < 0.001$; OR: 0.37). Patients who reported seizure clusters had on average an earlier age of seizure onset (17.5 ± 16.4 years old) compared to those who did not report seizure clusters (24.7 ± 19.7 years old; $P < 0.001$).

In the current study, 68 patients were followed up to death. In the 612 patients who had seizure clusters, 12 (2.0%) died; in the 3504 patients who did not have seizure clusters, 56 (1.6%) died. There was no difference in mortality noted between patients that had seizure cluster and those that did not ($P > 0.05$).

3.1. Benzodiazepine use

Patients who reported seizure clusters were more likely to be prescribed daily, standing use of benzodiazepine(s) chronically (23.9% vs 13.3%; $P < 0.001$; OR = 2.04, 95% CI: 1.66, 2.52) compared to patients without seizure clusters. Of the patients who had seizure clusters, 43.5% were prescribed at least one benzodiazepine rescue medication. 30.6% were prescribed 1 rescue medication, 10.8% were prescribed 2 rescue medications, and 2.1% were prescribed 3 or more rescue medications. Overall, 7.8% took rectal diazepam (DZP), 7.0% took oral DZP, 6.9% took intranasal midazolam (MDZ), 28.9% took oral lorazepam (LRZ), and 5.4% took oral clonazepam (CZP) (Table 1).

Table 1
Frequency of benzodiazepine rescue medication use for patients with seizure clusters by epilepsy type.

	Epilepsy Type				
	Focal (n = 475)	Idiopathic Generalized (n = 47)	Symptomatic Generalized (n = 65)	Unknown (n = 25)	All Seizure Types (n = 612)
Overall	199 (42.9%)	20 (42.6%)	39 (60.0%)	8 (32.0%)	266 (43.5%)
Diazepam (Rectal)	25 (5.3%)	2 (4.3%)	20 (30.8%)	1 (4.0%)	48 (7.8%)
Diazepam (Oral)	31 (6.5%)	6 (12.8%)	6 (9.2%)	0 (0.0%)	43 (7.0%)
Lorazepam (Oral)	144 (30.3%)	12 (25.5%)	15 (23.1%)	6 (24.0%)	177 (28.9%)
Midazolam (Intranasal)	28 (5.9%)	3 (6.4%)	8 (12.3%)	3 (12.0%)	42 (6.9%)
Clonazepam (Oral)	21 (4.4%)	5 (10.6%)	6 (9.2%)	1 (4.0%)	33 (5.4%)