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Identifying seizure clusters in patients with epilepsy

S. R. Haut, MD

From the Comprehensive Epilepsy Management Center, Department of Neurology, Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, NY.

R. B. Lipton, MD

From the Departments of Neurology, Epidemiology and Population Health, Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, NY.

A. J. LeValley, MA

From the Epidemiology and Population Health, Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, NY.

C. B. Hall, PhD

From the Departments of Neurology, Epidemiology and Population Health, Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, NY.

S. Shinnar, MD, PhD

From the Comprehensive Epilepsy Management Center, Departments of Neurology and Pediatrics, Montefiore Medical Center and the Albert Einstein College of Medicine, Bronx, NY.

Abstract

Clinicians often encounter patients whose neurologic attacks appear to cluster. In a daily diary study, the authors explored whether clustering is a true phenomenon in epilepsy and can be identified in the clinical setting. Nearly half the subjects experienced at least one episode of three or more seizures in 24 hours; 20% also met a statistical clustering criterion. Utilizing the clinical definition of clustering should identify all seizure clusterers, and false positives can be determined with diary data.

Many neurologic disorders are characterized by recurrent attacks and an enduring predisposition to attacks. For these chronic disorders with episodic manifestations (CDEM) including epilepsy, migraine, and multiple sclerosis, clinicians and patients seek explanations for the occurrence and patterns of attacks in hopes of being able to predict and prevent them. The fundamental question is whether the occurrence of attacks in these disorders is random or patterned. Epilepsy is uniquely suited to address the issue of clustering, as it appears that for some individuals (clusterers), the probability of a seizure is greater in the setting of recent seizures. Furthermore, many patients with epilepsy have a sufficient frequency of episodes to enable an evaluation of temporal patterns.

If clustering truly exists, then in a seizure clusterer, for example, the onset of a cluster requires aggressive intervention to prevent the short-term recurrence of additional seizures or status

Correspondence to: S. R. Haut.

Address correspondence and reprint requests to Dr. Sheryl R. Haut, Epilepsy Management Center, Montefiore Medical Center, 111 East 210th St., Bronx, NY 10467-2490; e-mail: haut@aecom.yu.edu.

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epilepticus. Additionally, the identification of clusterers creates an opportunity to search for environmental or genetic risk factors that predispose to clustering.

We utilized a daily diary study to test the hypothesis that clustering is a true phenomenon in epilepsy, and that it can be identified in the clinical setting. We examined a simple clinical definition of clustering—three or more seizures within 24 hours^{1,2}—which a patient may self-report and is easy to apply, and compared this to the statistical definition of clustering as a significant deviation from a random temporal distribution.³⁻⁶ This approach will inform our investigations into the phenomenon of clustering in epilepsy and may be applicable to other chronic disorders with episodic manifestations.

Methods. Subject recruitment and consent has been described.² Eligible subjects were ≥ 18 years old, had localization related epilepsy; ≥ 1 seizure during the prior 12 months and were capable of independently maintaining a seizure diary. Subjects reporting ≥ 3 seizures every day were excluded, as the definition of clustering assumes an increase over the mean daily seizure frequency.

Data collection. Subjects were trained to maintain daily diaries, including times and characteristics of all seizures, hours of sleep, medication compliance, alcohol use, stress measurements, and menstrual status (figure E-1 on the *Neurology* Web site at www.neurology.org). Subjects noncompliant with daily diaries were asked to maintain monthly seizure calendars.

Of 134 subjects enrolled between November 2002 and September 2004, 35 (26%) returned no diaries, 12 (9%) returned one diary, and 87 (65%) returned more than one diary and were included in these analyses; of these, 16 (18%) had no seizures.

Epilepsy classification and seizure localization were assigned by a single epileptologist (S.H.) in accordance with ILAE criteria.⁷ Localization was considered unknown in subjects with normal or nonlocalizable EEG and MRI data and no/nonlocalizable inpatient epilepsy monitoring. Subject data was available for MRI (100%), interictal EEG (87%), and ictal EEG (65%).

Seizure clustering was defined using a standard clinical definition (three or more seizures in 24 hours) and a statistical definition which tested the hypothesis that seizures were randomly distributed in time, following a Poisson distribution characterized by an equal mean and variance. Clustering or regular periodic pattern would be deviations from this model. The variance of the number of seizures per day was compared to the mean rate of seizures per day using a *t* test statistic.⁸ A mean greater than variance estimate indicated a regular periodic pattern, whereas a greater variance indicated a clustered pattern.

Results. Demographic and seizure data for 87 diary compliant and 47 noncompliant subjects is presented (table 1). The groups did not differ significantly by age, sex, epilepsy classification/localization, epilepsy etiology, or site of care. Mean/median follow-up was 233 diary days (see table E-1 on the *Neurology* Web site at www.neurology.org).

Seizure distribution for the 87 diary-compliant subjects is presented (table 2). Thirty-seven subjects (43%) met either definition of clustering, whereas 50 subjects (57%) were nonclusterers. All 37 clustering subjects met the clinical definition, and 19 (22%) also met the statistical definition. Eighteen subjects (21%) met the clinical but not the statistical definition.

Overall median seizure rate was 0.07 seizures/day (SD 0.5). Median rate for nonclusterers by any definition was 0.03 seizures/day (SD 0.05), as compared to 0.3 seizures/day (SD 0.68) for those with any clustering ($p = 0.0001$). Median seizure rate for statistical clusterers was 0.37

seizures/day (SD 0.80) and for clinical (not statistical) clusterers was 0.14 seizures/day (SD 0.48) ($p = 0.007$).

Nine statistical clusterers (47%) experienced > 50% of seizures in clinical clusters, in contrast to four clinical (not statistical) clusterers (22%). No subject experienced all of their seizures in clinical clusters. The subject most closely approximating a pure clusterer had 11/12 seizures (92%) occurring in clusters (111 follow-up days), and met both clustering definitions.

Discussion. In many people with epilepsy, seizure frequency permits a quantitative assessment of temporal patterns, including clustering. In this study, we examined the distribution of seizures in a large cohort of subjects followed with daily seizure diaries, to assess the prevalence of clustering and refine a method for identifying seizure clusterers. We defined seizure clustering either clinically (three seizures in 24 hours) or statistically (deviation from a Poisson distribution).

We conclude that clustering in epilepsy is common. Nearly half of our subjects experienced some seizures in clinical clusters, and approximately 20% met the more conservative definition of statistical clustering. Surprisingly however, pure clustering is rare; no subject experienced all of their seizures in clinical clusters.

The reported prevalence of seizure clustering by clinical criterion has ranged from 14% to 61%.^{1,2,9} Although biased toward intractable epilepsy, our study population had a low median daily seizure rate of 0.07, likely representing a wider range of seizure control than previous studies. Similarly, our prevalence of statistical clustering (20%) is lower than prior statistically-based reports with smaller sample sizes, in which 45% to 92% of subjects had seizure patterns deviating from a Poisson process.^{3,6}

All subjects who met the statistical definition of clustering also met the clinical definition, suggesting that the statistical definition is highly specific for clustering. However, even with the statistical definition, false negatives may arise, related to low seizure rates or short follow-up. Alternately, the clinical method likely yields false positives or seizure clusters occurring by chance. Higher seizure rate was significantly associated with clustering by either definition.

Our study includes a large sample, wide range of seizure control, and long median follow-up. Study limitations include recruitment from an epilepsy center, with a bias toward intractable epilepsy, and subject noncompliance with the diaries. However, seizure clustering in the well-controlled population appears to be rare, and baseline characteristics of noncompliant subjects did not differ significantly from compliant subjects, making participation bias less likely.

In clinical practice, it is important to identify potential seizure clusterers, as these patients may require abortive therapies (i.e., parenteral benzodiazepines) and may be at higher risk of status epilepticus.¹⁰ We demonstrate here that self-reported seizure clustering defined as three or more seizures in 24 hours should identify all true clusterers, but will also identify false-positive clusterers with high seizure rates. The clinical use of seizure diaries may help to identify those subjects.

We also demonstrate that pure seizure clustering is rare. Rather than examine risk factors for being a “clusterer,” we plan to explore risk factors for entering a “period of vulnerability” to clusters. Candidate risk factors include changes in sleep or medication, metabolic derangement, stress, or menstruation. The benefit of identifying modifiable risks for seizure clusters is considerable.

Similarly, in other chronic neurologic disorders (particularly migraine), clustering of attacks may not be an individual characteristic as much as a phenomenon related to periods of

vulnerability. Ongoing investigation of variables related to clustering in epilepsy may serve to refine strategies for evaluation of episode occurrence for other chronic disorders with episodic manifestations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient characteristics

Characteristic	Diary-compliant subjects	Diary-noncompliant subjects
n	87	47
Median age, y	39.6	37.4
Sex		
Male	33	16
Female	54	31
Epilepsy localization		
Temporal lobe	37	13
Frontal lobe	8	5
Extratemporal other	9	6
Nonlocalizable	32	20
Site of care		
Faculty practice	46	17
Seizure clinic	41	30

Table 2

Number of subjects meeting the clinical or statistical definitions of seizure clustering

	Clinical definition		Total
	Yes	No	
Statistical definition			
Yes	19	0	19
No	18	50	68
Total	337	50	87