Seizure clustering during drug treatment affects seizure outcome and mortality of childhood-onset epilepsy

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To provide evidence of whether seizure clustering is associated with drug resistance and increased mortality in childhood-onset epilepsy, a prospective, long-term population-based study was performed. One hundred and twenty patients who had been followed since disease onset (average age 37.0 years, SD 7.1, median 40.0, range 11–42; incident cases) were included. At the end of the follow-up period, 26 (11 boys) of these patients (22%) had recorded clusters of seizures. Fourteen recorded pre-treatment clusters, including 10 patients with clusters as first seizures; and in 12 patients, clusters occurred during treatment. In these 12 patients, first clustering began after 16 (range 0–35; median 15) years of treatment. Compared with the patients without clusters, those with clusters more often had at least one seizure per week at the initial stage (63% versus 32%, \(P = 0.0178\)) and during the follow-up period (\(P\)-value varied from 0.0464 to 0.0064). Patients having seizure clusters during drug therapy were more likely to have drug resistant epilepsy compared to those not experiencing seizure clusters (42% versus 13%; \(P = 0.0102\)) and had a lower rate of entering 5-year terminal remission (\(P = 0.0039\)) and 5-year remission (\(P = 0.0230\)). In addition, the risk of death was significantly increased among patients with seizure clusters during drug therapy compared with those who had not experienced any clustering (42% versus 14%; \(P = 0.0299\) two-sided Fisher’s exact test). The risk ratio for patients with clusters was 3.49 (95%CI 1.25–9.78). In contrast, patients with seizure clustering prior to, but not during, treatment versus those with no clustering showed no difference in seizure outcome or mortality risk. In conclusion, clustering of seizures during treatment, but not prior to treatment, is associated with a poorer long-term seizure and mortality outcome.

Keywords: seizure clustering; pharmacoresistance; drug resistance; AEDs; remission

Abbreviations: AEDs = anti-epileptic drugs; CSP = cortical silent period; GTC = generalized tonic–clonic; SYRE = 5-year remission ever; SYTR = 5-year terminal remission

Introduction

Studies of the natural history of new-onset childhood epilepsy indicate that seizures can be controlled in up to two out of three patients (Sillanpää and Schmidt, 2006). However, seizure outcome varies considerably in the epilepsies, even between patients with seemingly the same epilepsy syndrome, and its determinants are largely unknown (Schmidt and Löscher, 2005). For an individual developing this disease, whether or not the seizures will cease is the key question. In addition, increased mortality has been reported for patients with symptomatic epilepsy (Nashef and Shorvon, 1997) and it is important for patients and physicians to know the individual risks of mortality. Although many factors may contribute to variability in seizures and the likelihood of mortality in individual patients, a number of retrospective studies on hospital-based series have suggested that seizure clustering may be one predictor of poor seizure outcome (Balish et al., 1991; Bauer et al., 1992; Haut et al., 1999; Bauer and Burr, 2006; Haut, 2006). In a recent review, Haut (2006) suggested that prospective data are needed to better identify the risks of seizure clustering, and so to provide evidence of whether seizure clustering is associated with drug resistance and increased mortality, a prospective, long-term population-based study was performed.
Methods

Patients

Subjects were children aged 15 years or less who were living in the catchment area of the University of Turku Central Hospital, Turku, Finland, at the end of 1964 and who met the criteria for epilepsy (two or more unprovoked seizures) (Commission on Classification and Terminology of the International League Against Epilepsy, 1981; Central Statistical Office of Finland, 1989; Commission on Epidemiology and Prognosis of the International League Against Epilepsy, 1993). Subjects were identified on the basis of hospital, institution and primary health care records, and a review of the National Health Service records (a registry of all patients residing in Finland). Altogether, 245 patients were identified, 223 (91%) of them were seen in the University of Turku Central Hospital. The remaining 22 patients (9%) were seen in other hospitals, institutions and public or private primary or outpatient care offices. In Finland, in the 1960s, the practical guideline was to refer children with an epileptic seizure for evaluation. Untraceable and subsequently beyond the study were three more patients who, under ongoing surveillance, were identified and who met the inclusion criteria. Thus, the patient sample represents a population-based cohort of children aged 0–15 years with epilepsy.

The 245 patients included 150 (61%) who were first evaluated for epilepsy from January 1, 1961 to December 31, 1964 (incident cases). The remaining 95 patients (39%) had been seen for epilepsy both before and during the study period of 1961 to 1964. They had had active epilepsy (one or more seizures in the preceding three years before evaluation) during the study period (prevalent cases). All 245 patients had been examined and evaluated by one child neurologist (Sillanpää, 1973) and enrolled on a prospective follow-up of medical and social outcomes for a further 35 years. Follow-up included an ongoing review of the medical records and a comprehensive evaluation at 5-year intervals. In 1992, in addition to the structured extensive questionnaires, the evaluation included clinical examination completed with appropriate tests for physical fitness and laboratory investigations. The study design and some earlier results have previously been reported in detail (Sillanpää, 1973; Sillanpää et al., 1998, 1999, 2004; Sillanpää and Shinnar, 2002).

For the present study, 120 of the 150 incident cases, who had been followed since the onset of epilepsy, were included. All patients who had at least one cluster of three or more seizures within a period of 24 h—whether within 1 or over 2 days—were included. The majority had only one episode of clustering. Excluded from the analysis were patients with three or more seizures per day associated with West syndrome, Lennox–Gastaut syndrome, absence or myoclonic epilepsy, status epilepticus or autoinduced seizures separated by intermittent recovery. The reasons for the exclusion of 30 patients are listed in Table 1. Also excluded were children with episodes of status epilepticus lasting >30 min without the patient fully regaining consciousness (Dodson et al., 1993; Commission on Classification of and Terminology of the ILAE, 1989; Sillanpää and Shinnar, 2002), but not cases which had both episodes of status epilepticus and clustering of seizures with intermittent full recovery. Relapse was defined as the occurrence of repeated seizures after a patient had entered remission of 5 years or more. Relapse was also considered in conjunction with planned discontinuation of anti-epileptic drugs (AEDs) for patients in remission. A single seizure, however, including those prompted immediately by drug withdrawal, poor compliance or one occasion-related seizure, was not classified as a relapse. Accordingly, patients with a single seizure continued to be classified as being in remission. Compliance in temporal relation to clustering of seizures was determined by questioning the patient. Drug compliance was termed good if the patient answered: ‘Yes, according to the given instructions’ to the question: ‘Have you taken your drugs regularly?’. The other options were: ‘Yes, regularly, but less than instructed’; ‘I have occasionally forgotten medication’; ‘I have taken the medication irregularly’; ‘There have been longer breaks in the medication’; ‘I have spontaneously discontinued the medication’.

Definitions

Epileptic syndromes, epilepsies, epileptic seizures and aetiology of seizures were defined according to the guidelines for epidemiologic research of the International League Against Epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy, 1981; Central Statistical Office of Finland, 1989; Commission on Epidemiology and Prognosis of the International League Against Epilepsy, 1993). Random generalized epilepsy was defined as epilepsy with generalized tonic–clonic seizures (GTC) randomly distributed during the sleep–wake cycle as described by Janz (1969). Remission of epilepsy was defined as a seizure-free period of 5 or more consecutive years as suggested in the literature (Annegers et al., 1979). Terminal remission was the term used for remission at the end of follow-up. Epilepsy was called drug-resistant if remission was not achieved during a follow-up of at least 10 years despite adequate treatment. Seizure clustering was defined clinically, in agreement with Haut et al. [2000], as episodes of 3 or more afebrile seizures during a 24 h period.

Statistical analysis

For statistical analyses, the Pearson’s $\chi^2$-test with Fisher’s exact test (two-tail) and Yates’s correction when appropriate, Student t-test and Mann–Whitney test, Kruskall–Wallis test, stepwise logistic regression and Kaplan–Meier method were used. A $P$-value of <0.05 was considered statistically significant.
Statistical computations were done using SAS System for Windows, release 8.02 (SAS Institute, Cary, NC, USA). The study design was approved by the Joint Ethics Review Committee of the University of Turku and the University Central Hospital of Turku.

## Results

### Long-term seizure outcome

At the end of a 37-year follow-up (SD 7.1, median 40.0, range 11–42), 88 (73%) of 120 patients were in terminal remission, 16 (18%) of 88 were on AEDs and 72 (82%) were off AEDs, while 32 (27%) of 120 either never experienced a 5-year remission (5-YR) (i.e. were drug-resistant, 15%) or were not in terminal remission (but had previously had one or more 5-YRs, 12%).

### Seizure clustering

Among 120 patients, seizure clustering was noted in 26 patients (22%). Among the 26 patients, 14 recorded pre-treatment clusters, including 10 patients with clusters as first seizures; and in 12 patients, clusters occurred during treatment. In these 12 patients, first clustering began after an average of 16 (range 0–35; median 15) years of treatment. Four patients had a number of clusters during treatment. The long-term seizure outcome of patients experiencing seizure clustering during drug treatment was poorer than in those without seizure clustering. Fewer patients with clusters reached 5-year terminal remission (5-YTR) compared to those without clusters (33% versus 77%; \( P = 0.0230 \), Fig. 2). Furthermore, more patients with seizure clusters during treatment had drug resistant epilepsy compared to those without clusters (42% versus 13%; \( P = 0.0102 \)).

#### Table 2 Clinical features of patients with clusters of seizures (\( n \))

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cluster before drug treatment (( n = 14 ))</th>
<th>Cluster during drug treatment (( n = 12 ))</th>
<th>No of clusters (( n = 94 ))</th>
<th>Total</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>7</td>
<td>6</td>
<td>51</td>
<td>64</td>
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<tr>
<td>Female</td>
<td>7</td>
<td>6</td>
<td>43</td>
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<tr>
<td>Age at onset</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(&lt; 6 ) years</td>
<td>11</td>
<td>8</td>
<td>64</td>
<td>83</td>
</tr>
<tr>
<td>(&gt; 6 ) years</td>
<td>3</td>
<td>4</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>Epilepsy syndrome</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Localization related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>1</td>
<td>0</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Rolandic</td>
<td>1</td>
<td>0</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>5</td>
<td>9</td>
<td>51</td>
<td>65</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>3</td>
<td>6</td>
<td>34</td>
<td>43</td>
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<tr>
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<td>Occipital lobe</td>
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<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Not localizable</td>
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<td>2</td>
<td>13</td>
<td>17</td>
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<tr>
<td>Cryptogenic</td>
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<td>5</td>
<td>7</td>
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<td>Generalized</td>
<td>4</td>
<td>2</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>4</td>
<td>2</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Awakening</td>
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<td>1</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Random</td>
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<td>11</td>
<td>15</td>
</tr>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

We found no correlation between the choice of chronic AED treatment and clustering when we analysed a subgroup of patients with a 45-year follow-up. Comparison between cluster and non-cluster patients showed that 6/6 cluster patients and 14/22 non-cluster patients had two or more AEDs in daily use (\( P = 0.1412 \)). The AEDs used for treatment were: carbamazepine, clonazepam, vigabatrin, lamotrigine, oxcarbazepine, phenytoin, primidone and valproate. There was no significant difference between cluster and non-cluster patients (\( P = 0.4039 \)) with regard to the type or number of AEDs administered, nor was there any difference in AEDs use between patients with pretreatment clusters once they received AEDs and treatment clusters.

Patients who had a cluster as their first seizures were almost significantly younger (mean 2.90 versus 4.84, median 1.0 versus 3.0 years; \( P = 0.0577 \), Mann–Whitney) than patients without clusters. All patients had clusters exclusively either before or after starting treatment. Four patients had a number of clusters during treatment. Drug discontinuation was recorded in 12 of 14 with pre-treatment clusters and in 2 of 12 with clusters during treatment. None of the patients had clusters after the drug was tapered off. Three had a recurrence of clusters during the early and later course of their epilepsy, and one had a recurrence only late in the course of the treatment. None of the patients had all their seizures manifesting as clusters.

Of the 12 patients with clusters during treatment, one reported discontinuation of medication together with alcohol abuse, four had definitely ruled out precipitating events in temporal relationship to the occurrence of seizure clusters, in three we have no indication of precipitating factors and data are lacking on four patients.
often one or more weekly seizures during the first 12 months after onset of epilepsy (32% versus 72%; \( P = 0.0078 \)). In logistic regression analysis, the probability of clusters was significantly higher in patients with high seizure frequency at onset of epilepsy [odds ratio (OR) 4.6; 95%CI 1.09–19.23] and drug resistance (OR 4.1; 95%CI 1.01–16.38). Compared with patients without clusters, patients experiencing clusters any time in the course of their disorder more often had at least one seizure per week at the onset of epilepsy defined as two or more unprovoked seizures (63% versus 32%; \( P = 0.0178 \)). The association continued to be significant throughout the follow-up when reviewed in subsequent 5-year periods, with the \( P \)-value varying between 0.0464 and 0.00064.

One additional feature was that seizures on successive days were noted in two of three patients with recurrent clusters, but in only one of 23 patients without recurrent clusters. Occurrence of clusters whether before or during treatment was very significantly (\( P = 0.0002 \) versus \( P < 0.0001 \)) associated with periods of daily seizures. However, the overall occurrence or not of clusters prior to and during treatment was not significantly associated with seizure outcome, either 5YTR (\( P = 0.1925 \)) or 5YRE (\( P = 0.1244 \)), or aetiology (sympt, cryptog, idop) (\( P = 0.3910 \)) or partial versus generalized seizure type (\( P = 0.2860 \)), or age at onset (\(<6 \) or \( \geq 6 \) years) (\( P = 0.6257 \)). The presence of clustering was not associated with a higher risk of status epilepticus. Patients with pre-treatment clusters had episodes of status epilepticus in 2 (14%) of 14 cases and patients with clusters during treatment had status epilepticus in 5 (42%) of 12 cases.

**Mortality outcome in patients with seizure clustering**

The risk of death was significantly increased among patients with clustering during AED treatment compared with those without clusters ever (42% versus 14%; \( P = 0.0299 \) two-sided Fisher’s exact test, Fig. 3).

The risk ratio for patients with clusters versus those with no clusters ever (including clusters prior to and during treatment) was 3.49 (95%CI 1.25–9.78). However, the risk for death of patients with clusters prior to and during drug treatment was not significantly increased (19% versus 14%; \( P = 0.5379 \), two-sided Fisher’s exact test). The cause of death was determined by autopsy in all cases. The causes of death were: one from dissection of aorta; one from pneumonia; one from accidental drowning and two from SUDEP, defined according to Nashef and Shorvon (1997). The risk for death from SUDEP was higher in patients with clusters than in those without clusters, but the difference is not significant (8% versus 3%; \( P = 0.2215 \), two-sided Fisher’s exact test). An epileptic seizure could not be shown to be associated with the cases of SUDEP. None of the patients with pre-treatment clusters died. Five of the patients with clusters died during treatment; in three cases, the cause was considered to be epilepsy related (two cases of SUDEP and one with accidental drowning associated with a seizure), and in the remaining two patients, it was non-epilepsy related (one pneumonia and another cardiovascular failure). None of patients with clusters died from status epilepticus.

**Discussion**

In our prospective population-based study of new onset epilepsy in childhood with a long term average follow-up of
controls (Bauer refractory epilepsy. A 30% rate has been reported in more bias towards patients with higher seizure frequency and percentages may reflect the effect of planned medication 2002; Yen et al. higher. They ranged from 47% to 61% (Haut based patient samples, the rates of seizure clustering were clusters have a less favourable mortality outcome (see text). Fig. 3 Mortality of patients with and without seizure clustering on medication. The data indicate that patients experiencing seizure clusters have a less favourable mortality outcome (see text).

37 years, 26 of 120 patients (22%) had recorded clusters of seizures. In earlier studies in heterogeneous, mostly hospital-based patient samples, the rates of seizure clustering were higher. They ranged from 47% to 61% (Haut et al., 1999, 2002; Yen et al., 2001; Rose et al., 2003). These high percentages may reflect the effect of planned medication withdrawal or refractory epilepsy in monitoring units and a bias towards patients with higher seizure frequency and refractory epilepsy. A 30% rate has been reported in more heterogenous patient populations with a range of seizure controls (Bauer et al., 1992; Newmark and Dubinsky, 1990; Manford et al., 1996; Haut et al., 2005). In our population-based study of childhood-onset epilepsy with complete seizure control in about 67% of cases at the end of follow-up, only 22% (26/120) had clusters, including 14 of 26 patients with clusters exclusively before drug therapy and 12 patients only during drug treatment. The extent of clustering in a population-based study including previously untreated patients has not previously been documented. Finally, none of our 26 patients had clusters both before and during treatment. Compared with the patients without clusters, those with clusters more often had at least one seizure per week at the initial stage (63% versus 32%; \( P = 0.0178 \)) and during follow-up (\( P \)-value varying between 0.0464 and 0.0064).

Our main finding is that patients with seizure cluster occurring during drug therapy less often achieved 5-YTR (\( P = 0.0039 \)) and 5-YR (\( P = 0.0230 \)). Logistic regression analysis showed that a patient with seizure clustering during treatment compared to a patient without seizure clusters is four times more likely to experience drug resistant epilepsy. In addition, the risk of death was significantly increased among patients with clustering during AED therapy compared with those without clusters (42% versus 14%; \( P = 0.0299 \) two-sided Fisher’s exact test).

The risk ratio for patients with clusters was 3.49 (95%CI 1.25–9.78). We found one study in the literature which showed that in 57% of sudden unexplained deaths, patients had a history of seizure clustering (Nei et al., 2004). Unfortunately, seizure cluster data were not available from comparison patients (Nei et al., 2004). In contrast, patients with seizure clustering prior to treatment versus no clustering showed no difference in seizure outcome or mortality risk. We conclude that clustering of seizures during treatment is associated with a poorer long-term seizure and mortality outcome, while seizure clustering prior to treatment is not associated with poor seizure or mortality outcome. Three questions need to be addressed. One, what are potential causes for poorer seizure and mortality outcome in patients with clustering during treatment; two, why is having clusters during treatment more disadvantageous compared to pre-treatment clustering or having no clusters? Three, what are the implications of our findings for management of epilepsy and epilepsy research?

Clustering has been suggested in the literature to be one marker for worse seizure control (Balish et al., 1991; Haut et al., 1999). Our study confirms this observation in a population-based study of new onset childhood epilepsy for clustering during treatment. Possible explanations for the increased risk of having refractory epilepsy with poor seizure control in patients with clusters include an association of seizure clustering with a higher frequency of seizures and a history of convulsive status epilepticus that has been reported before and confirmed by us (Manford et al., 1996; Regesta and Tanganelli, 1999; Haut, 2005). The mechanism underlying the generation of seizure clustering is not known (Haut, 2006). Using transcranial magnetic stimulation, a preliminary study of six patients, including five patients with partial epilepsy, experiencing perimenstrual seizure clustering showed a shorter cortical silent period (CSP) during the luteal phase and menstruation as compared to the follicular phase. According to the authors, the CSP changes suggest a decreased inhibition involving GABA-ergic neurotransmission (Hattemer et al., 2006). Further studies including male patients with seizure clustering are needed.

Our finding that seizures occur in clusters prior to treatment has not been reported before. Previous studies on clustering were performed in chronically treated patients. All patients with pre-treatment clusters stopped having clusters during treatment. Furthermore, pre-treatment clusters had no association with poor seizure outcome compared to patients without clustering. In the study of Shinnar et al. (1996), the seizure outcome after episodes of multiple initial unprovoked seizures did not differ from that after one initial seizure. The lack of impact is also comparable with an episode of afebrile status epilepticus as a first seizure, which did not significantly affect the seizure outcome (Shinnar et al., 1996; Sillanpää and Shinnar, 2002).
The finding that no subjects in our study had clusters both before and during or after treatment in our study is unexpected, given prior literature that suggests that some persons with epilepsy tend to cluster and some do not. One might have expected that patients with clusters during treatment started with clusters prior to treatment. We found only one study in the literature, which has examined the temporal onset of first clustering in epilepsy (Bauer et al., 1992). In an epilepsy clinic-based study of 60 clusterers with temporal lobe epilepsy, the majority those having clusters during treatment (46/60) did not have pre-treatment clusters but developed treatment-emergent clusters after an average of 16.5 years (range 1–50 years).

Although the authors did not compare seizure outcome in initial versus later clusterers, the observation that clusters were first noted after many years on AEDs suggests that the epilepsy was refractory. Also, the authors reported that a higher proportion of patients with treatment emergent clusterers initially had tonic–clonic seizures at the onset of their partial epilepsy and only in the course of the disorder (and the treatment), did drug resistant complex partial seizures supervene (Bauer et al., 1992). In our incident population, clustering was first seen after an average of 16 years of treatment.

In more refractory populations as in our series of prevalent cases, 3/24 had clusters both before and during AED treatment, versus 0/26 in the incident series. Possibly because of small patient numbers, the difference was not statistically significant ($P = 0.1033$), although it was not far from that. Retrospective hospital-based studies of prevalent cases or a mixture of incident and prevalent cases in the literature with a bias towards refractory epilepsy may have created the impression that a patient is either a clusterer from the start of epilepsy or not. Based on our data, we disagree and suggest that the onset of clustering in a patient with epilepsy may first occur years into the course of the epilepsy and indicate a period of vulnerability that is associated with poor seizure control. The clinical implications of this unexpected finding are discussed subsequently.

We found increased mortality in our incident cohort which is clinically important as our population is not biased towards refractory epilepsy, which is well known to be associated with increased mortality (Nashef and Shorvon, 1997). What is the relevance of this knowledge and how may it impact clinical practice? Although an association of clustering with convulsive status epilepticus has been reported in retrospective series, which used a much more restricted definition of clustering of at least 50% of all seizures occurring in clusters (Haut et al., 1999), the finding was not confirmed in other studies by the same group (Haut et al., 2002). We did not find an association of clustering with convulsive status epilepticus, and mortality associated with status epilepticus was not more common in seizure clusterers. The pathophysiological link between increased mortality and seizure clustering is not clear. Whatever the mechanism, it is worthwhile to evaluate if medical prevention of seizure clustering is able to lower the mortality of clusterers with epilepsy.

Our study is the first population-based study with a wide range of seizure control and a very long median follow-up. Study limitations include that false negatives may arise due to low seizure rate, while false positives may be related to high seizure frequency or chance seizure clusters. Also, precipitating factors or their absence were not always documented for each observed cluster. In our study, as in the literature, a higher seizure rate was significantly associated with clustering. Understanding the mechanisms behind clustering may provide important therapeutic insights into potentially altering the outcome of seizure progression in patients with temporal lobe epilepsy. In that respect, it is unfortunate that many controlled trials of experimental AEDs in patients with partial seizures exclude seizure clusterers, possibly to simplify assessment of seizure rates during the trial. Drug trials in seizure clusterers may possibly give insight into the ability of an AED to affect the progression of seizures. Our results indicate that patients reporting clustering are at a higher risk of experiencing poorer seizure outcome and an increased mortality rate. Aggressive drug treatment and abortive treatment of clusters should be considered. If such a treatment is able to improve the course of epilepsy and to lower mortality remains to be seen.

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