

## PATIENTS WITH SEIZURE CLUSTERS—IDENTIFICATION OF A HIGH-RISK GROUP

### Seizure Clustering During Drug Treatment Affects Seizure Outcome and Mortality of Childhood-Onset Epilepsy.

Sillanpää M, Schmidt D. *Brain* 2008;131(Pt 4):938–944. 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.

### COMMENTARY

More than a century ago, Gowers recognized seizure clustering as a pattern exhibited by many people with epilepsy (1). Seizure clustering patterns imply a nonrandom occurrence of seizures such that a subsequent seizure depends, at least in part, on whether a person has had a recent seizure. Clustering of seizures provided early evidence that hormones and the time of day influence seizure susceptibility (2). More importantly, recognition of clustering has resulted in successful treatment strategies aimed at reducing the risk of subsequent seizures (3,4). Although seizures occurring in rapid succession might seem ominous, the extent of the risk posed by this pattern has not been studied extensively. Observations suggest that seizure clusters often result in emergency room visits (2) and that they may lead to status epilepticus (5). In the current study, Sillanpää and Schmidt provide preliminary evidence that seizure clusters occurring during anticonvulsant treatment are also associated with increased mortality and portend a poor prognosis for long-term seizure control.

The authors used National Health Service records from Finland to identify all children (aged 15 and younger) who had developed epilepsy by the end of 1964. Seizure clustering was defined clinically to be three or more seizures, during any 24-hour period, on at least one occasion. Patients were excluded from analysis if they had conditions with expected seizure clus-

tering, such as Lennox-Gastaut syndrome, infantile spasms, and absence or myoclonic seizures. Patients were considered drug-resistant if they had not entered a 5-year remission during the 10 or more years of follow-up. The authors emphasize that their cohort represents a true population-based sample since standard practice in Finland in the 1960s dictated that all children with epilepsy be referred to Dr. Sillanpää. In contrast to studies arising from tertiary epilepsy programs that treat only medically refractory patients, this study is likely to be relevant to the practice of most community-based neurologists.

Statistical comparisons were not designed to determine whether the mortality and seizure control outcomes were independent. As the authors note, medication-refractory epilepsy is known to be associated with increased mortality (6). It is certainly possible that the increased risk of death is attributable to poorer overall seizure control in patients who have seizure clusters—rather than seizures occurring in succession. Supporting this possibility is the fact that patients with seizure clusters did not die from status epilepticus, a mechanism potentially associated with clustering (5), but instead from sudden unexpected death in epilepsy, or SUDEP, which is known to be associated with drug-resistant epilepsy (7).

The current study is limited by the small number of patients who exhibited a clustering pattern. Given the limited power of the study, the finding that seizure clustering is not associated with an increased risk for status epilepticus will need to be confirmed by a larger study, especially since 5 of the 12 patients with seizure clusters during treatment had episodes of status

epilepticus. An additional consequence of the limited number of clustering patients in this study is a large confidence interval for the risk ratios for mortality and intractability, suggesting that it is premature to use these specific values to counsel patients with this seizure pattern. Nevertheless, it seems reasonable to counsel patients that a clustering pattern probably confers at least some risk for these outcomes.

Another limitation of the Sillanpää and Schmidt report is that they did not use a statistical model to ensure that patients who were designated as clusterers actually deserved that designation. Other investigators have found that using their clinical criterion of three seizures in 24 hours is too broad, as it allows inclusion of patients who meet this definition by chance (8). Use of a statistical model that demonstrates a seizure's dependency on prior seizures can ensure that the observed seizure-clustering pattern represents a physiological phenomenon. While limiting the identification of clustering to patients with such statistical clustering might have been informative, it would have been unfeasible in this study because of the small number of patients. Furthermore, a clinical definition offers clinicians practical guidance in identifying patients for purposes of counseling and modifying treatment.

Patients who have seizure clusters have been identified as ideal candidates for using rescue medications, such as rectal diazepam (3) and buccal midazolam (4). Though the association is uncertain, it is interesting to note that the incidence of generalized convulsive status epilepticus has decreased in California over the past decade, as use of rescue medications for seizure clusters has increased (9). It is unclear whether use of rescue medications for this population will have an impact on mortality, however. Since the cause of death for patients with seizure clusters was not attributed to status epilepticus in the Sillanpää and Schmidt study, it seems clear that rescue medications will not completely eliminate the mortality associated with a clustering seizure pattern.

In summary, Sillanpää and Schmidt have raised awareness of seizure clustering as a risk for poor seizure control and mortality. While the practical implications are not clear, the findings may indicate a need for more aggressive management in patients exhibiting this pattern. Studies powered to confirm and extend the outcomes would be desirable and are necessary before the findings can be used to counsel patients about specific risks.

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## References

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