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Brief Communication

The Association Between Seizure Clustering and Convulsive Status Epilepticus in Patients with Intractable Complex Partial Seizures

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Summary: *Purpose:* We examined the association between seizure clustering and convulsive status epilepticus (SE) in patients with intractable complex partial seizures, to identify whether patients whose seizures typically cluster are at high risk for convulsive SE (CSE).

Methods: Seventy-six patients with intractable complex partial epilepsy who underwent presurgical evaluation in the Montefiore Epilepsy Management Unit from 1993 to 1997 were contacted and interviewed about typical seizure frequency and distribution and history of CSE. Seizure clustering was defined as three or more complex partial seizures within a 24-h period, with return to baseline between seizures.

Results: Of the 76 patients contacted, 21 (28%) had experienced at least one episode of CSE, and 36 (47%) typically experienced clustered seizures. SE occurred in 16 (44%) of 36 patients with clustered seizures, and in five (12.5%) of 40 patients with nonclustered seizures ($p < 0.002$). Of 53 patients with temporal lobe epilepsy, CSE occurred in 13 (50%) of 26 patients with clustered seizures, and four (14.8%) of 27 patients with nonclustered seizures ($p < 0.006$).

Conclusions: Patients with intractable complex partial or localization-related epilepsy who typically experience seizure clustering are at a significantly higher risk for CSE than are patients with nonclustered seizures. **Key Words:** Clustered seizures—Status epilepticus—Intractable epilepsy—Partial seizures—Temporal lobe epilepsy.

Patients with intractable complex partial epilepsy or intractable localization-related epilepsy frequently experience seizures that occur in "clusters" or flurries. Although some patients have seizure clustering only during an acute illness or anticonvulsant discontinuation, many patients regularly experience clustered seizures (1). We have previously analyzed seizures occurring during long-term video-EEG monitoring, and reported that seizures that occurred in clusters, with <8 h separating consecutive events, were not truly independent (2). If seizure clustering represents persistent irritability or decreased inhibition at a single focus, then patients whose seizures typically cluster may be at higher risk for status epilepticus than are those patients who do not experience seizure clustering. If this is so, it may have implications for therapy. We therefore examined the association between seizure clustering and convulsive status epilepticus (CSE) in patients with intractable complex partial seizures.

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MATERIALS AND METHODS

Patient identification and selection

One hundred forty-nine patients with intractable complex partial seizures or intractable localization-related epilepsy were monitored for presurgical evaluation in the Montefiore Epilepsy Management Unit from 1993 to 1997. At least two standard antiepileptic drugs (AEDs) had failed for all patients, and three or more antiepileptics drugs had failed for the majority.

Patients and/or family were called and questioned as to the patient's typical seizure frequency, and history of CSE. To increase reliability of reporting, both patient and family were interviewed whenever possible.

Seizure clustering was defined as three or more seizures occurring within 24 h, with recovery to clinical baseline between seizures. Patients were considered to have typically clustered seizures only if they reported that ≥50% of their seizures occurred in clusters.

Status epilepticus was defined according to the ILAE guidelines, as ≥30 min of consecutive seizure activity, or two or more repetitive seizures without full recovery of consciousness between seizures (3). To increase reliability of reporting, only episodes of generalized CSE were included. Episodes of CSE associated with abrupt medication discontinuation or fever were excluded.

Statistical methods

The relation between seizure clustering and CSE was examined by using univariate analysis, with Mantel–Haenszel correction when appropriate and Fischer's Exact text (two-tail). This method was thought to be most appropriate, as both the presence or absence of seizure clustering and the presence or absence of CSE were treated as dichotomous variables. For all analyses performed, a p value of <0.05 was considered statistically significant. All p values are two-tailed (4,5).

RESULTS

Of 149 patients monitored, 76 (51%) were successfully contacted and interviewed. The age of the patients is reflected in Table 1. Overall, 21 (28%) of 76 patients had experienced at least one episode of CSE, and 36 (47%) of 76 patients typically experienced clustered seizures. CSE had occurred in 16 (44%) of 36 patients with seizure clustering and in only five (12.5) of 40 patients without seizure clustering ($p < 0.002$, Table 2).

Ictal recordings were reviewed in all cases to determine seizure localization. Seizure onset was based on 60 extracranial and 16 intracranial recordings, and was localizable in 67 of 76 patients. In the remaining nine patients, seizure onset could not be determined from review of the surface ictal recordings. Seizure onset was temporal in 53 patients, frontal in 11 patients, occipital in two patients, and parietal in one patient. Of the 53 patients with temporal lobe seizures, CSE had occurred in 13 (50%) of 26 patients with clustered seizures and in four (14.8%) of 27 patients without clustered seizures ($p < 0.006$). Of the 11 patients with frontal lobe seizures, CSE had occurred in three (50%) of six patients with clustered seizures and none of five patients without clustered seizures (Table 3).

TABLE 1. *Patient age*

Age (years)	Number of patients
10–15	4
16–20	9
21–35	28
36–50	28
>50	7

TABLE 2. *All patients*

	Convulsive SE		
Seizure clustering[a]	Yes	No	Total
Yes	16	20	36
No	5	35	40
Total	21	55	76

[a] $p < 0.002$.

DISCUSSION

These results demonstrate that in patients with intractable complex partial seizures or intractable localization-related epilepsy, a significant association exists between the occurrence of seizure clustering and CSE. This association was seen both overall and in the subgroup of patients with documented temporal lobe epilepsy. Although the number of subjects with extratemporal epilepsy is too small to analyze meaningfully, the results in this group are similar. Seizure clustering has been proposed to predominate in extratemporal epilepsy, particularly in frontal lobe epilepsy, and this is currently being prospectively addressed. It is possible that patients with particular epilepsy types are more likely to experience both CSE and clustered seizures.

The pathophysiology of SE is complex and much remains poorly understood. As recently discussed by Treiman et al. (6,7), most seizures are brief and are followed by a refractory period. The mechanism of SE is understood to be a failure of seizure-terminating mechanisms, perhaps related to a loss of γ-aminobutyric acid (GABA)-mediated inhibition, or excessive glutaminergic excitation (8). Seizure clustering may represent a similar deficiency in seizure termination. This study suggests that seizure clustering is an indicator of pathophysiology that also predisposes to SE.

The degree of postictal suppression and refractoriness after a seizure in animal models has been demonstrated to increase with increasing age, one factor that may con-

TABLE 3. *Patients with known localization*

	Convulsive SE		
Seizure clustering	Yes	No	Total
Temporal lobe onset[a]			
Yes	13	13	26
No	4	23	27
Total	17	36	53
Frontal lobe onset[b]			
Yes	3	3	6
No	0	5	5
Total	3	8	11

[a] $p < 0.006$.
[b] p nonsignificant by Fisher's Exact test.

tribute to the higher incidence of SE in youth (9). If the pathophysiology of seizure clustering resembles that of CSE, one may expect a similarly increased incidence of seizure clustering during youth, and this is being examined prospectively.

The study is limited by a dependence on patient reporting, which limits reliability. DeLorenzo et al. (10) recently reported that seizures with a duration of 10–29 min differed significantly from SE, and it is possible that some of the episodes of CSE reported by the patients in our study were actually seizures of 10–29 min. However, the ultimate goal of this study was to identify patients who may be at risk for prolonged seizures requiring emergency intervention, and patients who regularly experience clustered seizures appear to be at such a risk.

Clinicians who treat patients with intractable complex partial or localization-related epilepsy should be aware that patients whose seizures typically cluster are at a higher risk for CSE than other patients.

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