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Double, Double Toil and Trouble: Recurrent Episodes of Status Epilepticus Are Associated With Increasingly Worse Outcomes

Clinical Characteristics and Outcomes of Patients With Recurrent Status Epilepticus Episodes

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Background: Multiple studies have focused on medical and pharmacological treatments and outcome predictors of patients with status epilepticus (SE). However, a sufficient understanding of recurrent episodes of SE is lacking. Therefore, we reviewed recurrent SE episodes to investigate their clinical characteristics and outcomes in patients with relapses. Methods: In this retrospective, multicenter study, we reviewed recurrent SE patient data covering 2011 to 2017 from the university hospitals of Frankfurt and Marburg, Germany. Clinical characteristics and outcome variables were compared among the first and subsequent SE episodes using a standardized form for data collection. Results: We identified 120 recurrent SE episodes in 80 patients (10.2% of all 1177 episodes). The mean age at the first SE episode was 62.2 years (median 66.5; SD 19.3; range 21–91), and 42 of these patients were male (52.5%). A mean of 262.4 days passed between the first and the second episode. Tonic–clonic seizure semiology and a cerebrovascular disease etiology were predominant in initial and recurrent episodes. After subsequent episodes, patients showed increased disability as indicated by the modified Rankin Scale (mRS), and 9 out of 80 patients died during the second episode (11.3%). Increases in refractory and super-refractory SE (RSE and SRSE, respectively) were noted during the second episode, and the occurrence of a non-refractory SE (NRSE) during the first SE episode did not necessarily provide a protective marker for subsequent non-refractory episodes. An increase in the use of intravenous-available anti-seizure medication (ASM) was observed in the treatment of SE patients. Patients were discharged from hospital with a mean of 2.8 $\pm$ 1.0 ASMs after the second SE episode and 2.1 $\pm$ 1.2 ASMs after the first episode. Levetiracetam was the most common ASM used before admission and on discharge for SE patients. Conclusions: This retrospective, multicenter study used the mRS to demonstrate worsened outcomes of patients at consecutive SE episodes. ASM accumulations after subsequent SE episodes were registered over the study period. The study results underline the necessity for improved clinical follow-ups and outpatient care to reduce the health care burden from recurrent SE episodes.

Commentary

In this 2-center retrospective study, the authors investigated the features and outcome of patients with recurrent status epilepticus (SE).[1] The study focuses on first and subsequent episodes in the cohort of patients with recurring SE. Prior studies on the topic have compared all patients with single episodes of SE to patients with recurrent episodes of SE, thus introducing differences in etiology between groups.[2-5] Acute symptomatic SE for instance is less likely to recur than SE in the setting of remote epilepsy.[3]

The first key finding is that 10% of patients with a first episode of SE are at risk of suffering from a recurrent episode of SE, half of them within 6 months of the first episode. This figure is roughly in line with the available literature, which provides an estimate of recurrence ranging from 7.6% to 32%.[2-5] Thus, the annual risk of a second episode of SE after having suffered from a first is at least 250 to 1000 times higher than the annual incidence of SE in the general population.[6] Even though half of the episodes of SE occur in patients with epilepsy, a 10% annual risk is still higher than the risk of SE in patients with epilepsy.

This indicates an intrinsic predisposition of a subgroup of patients for their seizures to present as SE. The International League Against Epilepsy defines SE as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures."[7] While these mechanisms still elude us, an individual's predisposition for SE

suggests that this could be identified by investigating patients with recurrent episodes, at the neuroanatomical, neurophysiological, and, perhaps, genetic levels. The mean age of patients in the cohort was 62 years at the time of the first episode and 63 years at the time of the second episode. This is not surprising as SE incidence peaks after 60 years.[6] Part of it is explained by the higher incidence of acute brain injuries, such as ischemic strokes and cerebral hemorrhages, that can cause SE after 60 years. Since most patients in this cohort, and in other cohorts of recurrent SE, had remote epilepsy, it is also possible that this higher risk of SE and of SE recurrence is also in part explained by the aging of the brain, which could be accompanied by a decrease in the efficiency of the mechanisms responsible for seizure termination. The risk of SE is also higher in patients with drug-resistant epilepsy and uncontrolled seizures than in patients with controlled epilepsy. Whether this also affects the risk of recurrence is unclear, although a prior study found that recurrent episodes of SE were more likely in patients who took more anti-seizure medications (ASMs).[5]

A few patients in the cohort suffered 3 or more episodes of SE. From the data presented in the article, it can be estimated that the risk of third, fourth, or fifth episode approximates 50%, which is even greater than the risk of a first recurrence. This might mean that some individuals have a particularly strong intrinsic predisposition for SE. Another possible explanation is that each SE episode durably tampers the epileptic network to make it more prone to subsequent episodes. After all, the epileptogenic effects of SE are well-known: experimental SE, by chemical or electrical mean, is a classical way to cause epilepsy in animal models and acute symptomatic SE in acute brain injuries carries a greater risk of long-term post-injury epilepsy than single acute symptomatic seizures.[8]

The second key finding of the study is that recurring episodes of SE are associated with increasingly worse outcomes. Compared to a first episode, a second episode of SE carries a higher risk of functional decline and dependency. It also leads to an increase in the burden of anti-seizure medications, including with medications that have a less desirable profile of side effects in the elderly, such as phenytoin and valproate. However, at the time of the second episode, the mean number of ASMs taken was lower than immediately after the first episode. Although this was not formally assessed in this study, ASM withdrawal was previously identified a precipitating factor of recurrent SE.[3] The authors thus rightfully warn us against the temptation to quickly withdraw the ASM used to manage SE. Given the risk of recurrence, seizure action plans that could be used in the out-of-hospital setting should be discussed with patients and caregivers. Such plans may include fats-acting benzodiazepines for prolonged seizures.

There was also a trend toward increasing refractoriness at the time of the second episode. Of note, this has not been found in all other studies, perhaps owing to the difference in inclusion criteria mentioned above. A prior study found that the risk of refractoriness was higher if SE episodes recurred within 6 months of the first episode, but this was probably explained a greater proportion of acute and progressive etiologies in this subgroup.[4]

Overall, this study further draws attention to a subgroup of patients with recurring SE who require special attention. They are an experiment of nature that could help us better understand the mechanisms of SE and calls for further studies. They also represent a clinical challenge that can possibly be addressed by better prevention and careful management.

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References

1. Bauer K, Rosenow F, Knake S, Willems LM, Kämppi L, Strzelczyk A. Clinical characteristics and outcomes of patients with recurrent status epilepticus episodes. *Neurol Res Pract*. 2023;5(1):34. doi:10.1186/s42466-023-00261-9
2. Hesdorffer DC, Logroscino G, Cascino GD, Hauser WA. Recurrence of afebrile status epilepticus in a population-based study in Rochester, Minnesota. *Neurology*. 2007;69(1):73-78.
3. Tsetsou S, Novy J, Rossetti AO. Recurrence of status epilepticus: prognostic role and outcome predictors. *Epilepsia*. 2015;56(3):473-478.
4. Orlandi N, Gozzi A, Giovannini G, et al. Recurrent status epilepticus: clinical features and recurrence risk in an adult population. *Seizure*. 2022;97:1-7.
5. Gasparini S, Ferlazzo E, Gigli G, et al; Epilepsy Study Group of the Italian Neurological Society. Predictive factors of status epilepticus and its recurrence in patients with adult-onset seizures: a multicenter, long follow-up cohort study. *Seizure*. 2021;91:397-401.
6. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56(10):1515-1523.
7. Gilmore EJ, Hirsch LJ. Epilepsy: status epilepticus epidemiology—tracking a moving target. *Nat Rev Neurol*. 2015;11(7):377-378.
8. Sinka L, Abraira L, Imbach LL, et al. Association of mortality and risk of epilepsy with type of acute symptomatic seizure after ischemic stroke and an updated prognostic model. *JAMA Neurol*. 2023;80(6):605-613.