Acute Symptomatic Seizures After Ischemic Strokes: Time Is Brain, Squared!

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Association of Mortality and Risk of Epilepsy With Type of Acute Symptomatic Seizure After Ischemic Stroke and an Updated Prognostic Model

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Importance: Acute symptomatic seizures occurring within 7 days after ischemic stroke may be associated with an increased mortality and risk of epilepsy. It is unknown whether the type of acute symptomatic seizure influences this risk. Objective: To compare mortality and risk of epilepsy following different types of acute symptomatic seizures. Design, Setting, and Participants:: This cohort study analyzed data acquired from 2002 to 2019 from 9 tertiary referral centers. The derivation cohort included adults from 7 cohorts and 2 case-control studies with neuroimaging-confirmed ischemic stroke and without a history of seizures. Replication in 3 separate cohorts included adults with acute symptomatic status epilepticus after neuroimaging-confirmed ischemic stroke. The final data analysis was performed in July 2022. Exposures: Type of acute symptomatic seizure. Main Outcomes and Measures:: All-cause mortality and epilepsy (at least 1 unprovoked seizure presenting >7 days after stroke). Results: A total of 4552 adults were included in the derivation cohort (2547 male participants [56%]; 2005 female [44%]; median age, 73 years [IQR, 62-81]). Acute symptomatic seizures occurred in 226 individuals (5%), of whom 8 (0.2%) presented with status epilepticus. In patients with acute symptomatic status epilepticus, 10-year mortality was 79% compared with 30% in those with short acute symptomatic seizures and 11% in those without seizures. The 10-year risk of epilepsy in stroke survivors with acute symptomatic status epilepticus was 81%, compared with 40% in survivors with short acute symptomatic seizures and 13% in survivors without seizures. In a replication cohort of 39 individuals with acute symptomatic status epilepticus after ischemic stroke (24 female; median age, 78 years), the 10-year risk of mortality and epilepsy was 76% and 88%, respectively. We updated a previously described prognostic model (SeLECT 2.0) with the type of acute symptomatic seizures as a covariate. SeLECT 2.0 successfully captured cases at high risk of poststroke epilepsy. Conclusions and relevance:: In this study, individuals with stroke and acute symptomatic seizures presenting as status epilepticus had a higher mortality and risk of epilepsy compared with those with short acute symptomatic seizures or no seizures. The SeLECT 2.0 prognostic model adequately reflected the risk of epilepsy in high-risk cases and may inform decisions on the continuation of anti-seizure medication treatment and the methods and frequency of follow-up.

Commentary

Everyone with epilepsy has seizures, but not everyone with seizures has epilepsy! This maxim distills the difference between an unprovoked seizure in a person with epilepsy and an acute symptomatic seizure (ASyS). The latter is a symptom of a systemic or brain injury that immediately (acutely) precedes it. Based on expert opinion, the immediacy of the time period between injury and ASyS is etiology dependent, ranging from 24 hours (for systemic insults like electrolyte imbalance) to 7 days (acute brain injuries like strokes) or longer (coinciding with intracranial inflammation or infection signs).[1] The current clinical definition of epilepsy is heavily influenced by the discovery that the timing of the first seizure (within or after 7 days) after an acute stroke leads to significantly different risks of subsequent unprovoked seizure (33% vs 72%, respectively).[2,3] With remote symptomatic seizures becoming synonymous with new-onset epilepsy, ASyS may seem to be a "benign" transitory phenomenon, especially because of the

intuitive appeal of the concept of seizure risk reduction after reversing underlying etiology.[4] Most ASyS in the neurological practice are due to acute injuries such as stroke, trauma, and infection, which lead to chronic, static lesions. The abovementioned 33% risk of epilepsy development after stroke-related ASyS is not dissimilar to the risk after the first unprovoked seizure.[5] Therefore, it's no surprise that ASyS, convulsive or electrographic, is a critical prognostic marker of symptomatic epilepsy development.[6-8]

The disease burden of poststroke epilepsy (PSE) is substantial. It accounts for more than half of all new-onset epilepsy cases among older adults, making it the most common preventable epilepsy in this age-group.[9] To take initial steps toward the holy grail of epilepsy prevention requires reliable predictive models—*if we can predict it, (maybe) we can prevent it!* The SeLECT score, derived using a large multicenter European cohort of patients with ischemic stroke, was that breakthrough for PSE.[7] It is a weighted prognostic score, which includes stroke severity [based on National Institute of Health Stroke Scale (NIHSS)], large artery atherosclerosis, early seizure (ASyS), cortical involvement, and territory of the middle cerebral artery. Acute symptomatic seizure reigns supreme in the SeLECT score, contributing a third of the maximum possible score of 9. Given ASyS's critical contribution to increased epileptogenesis risk, the group behind the SeLECT score is now investigating if a convulsive or clinical seizure presenting as acute symptomatic status epilepticus (ASySE) has different prognostic association with mortality and epileptogenesis.[10]

The authors included 4522 patients with ischemic stroke (median age 73 years) collected using various selection methods from 9 international centers. Among them, 5% had ASyS, including 8 (0.2%) individuals with ASySE and the rest with short ASyS (less than 5 minutes). Using multivariable regression modeling (adjusted for age, sex, acute treatment [reperfusion therapy and anti-seizure medications], and SeLECT predictors), they found that apart from older age and stroke severity, short ASyS and ASySE were independently associated with increased mortality (hazard ratio [HR] of 3 [1.8-4.8] and 12.7 [3.0-52.7], respectively) compared to patients without ASyS. A similar PSE model developed using the 190 participants with known ASyS type (short vs ASySE) found that ASySE was the only significant predictor of epilepsy development (HR = 4.3 [1.3-13.9]). For ASySE patients in the abovementioned cohort, the predicted mortality risk at 2- and 10-year follow-ups was similar to the unadjusted risk in a curated cohort of 39 poststroke ASySE. However, the latter cohort had a higher predicted risk of PSE in the first 2 to 3 years of follow-up. The authors updated their SeLECT scoring model to include the contribution of ASyS type—short ASyS receive 3 points, and ASySE gets a whopping 7 points—with the maximum possible score of SeLECT 2.0 reaching 13.

Status epilepticus has 1-year mortality of 15% to 30% in adults, which increases with age.[11] The 30-day case fatality after ASyS is 20%.[12] A systematic review shows that ASySE increases mortality risk after stroke.[13] The current study expands the literature by its attempt to move past the binary, presence or absence, of ASySE. It highlights the contribution of acute seizure burden on mortality. The biological plausibility of the direct dose–response relationship of ASyS duration with mortality is previously noted for nonconvulsive seizures recorded on electroencephalogram.[14] Although the confidence in the effect size of ASySE's association with mortality is dampened due to only 8 patients with the condition (reflected by the large HR confidence intervals), its mere detectability in such a setting speaks to the strength of this association.

ASySE's association with increased risk of epilepsy development compared to short ASyS was previously reported using the Rochester Epidemiology Project's data from 1965 to 1984.[15] After adjusting for age, sex, and etiology, patients with ASySE (30 minutes or longer) had a 3.3 (1.8-6.1) times increased rate of epilepsy development.[15] It is difficult to apply this information when managing and counseling patients with particular etiologies. As mentioned above, the SeLECT score study for predicting PSE remains a momentous feat due to its scope, scale, and impact.[7] The only change in SeLECT 2.0 is that ASySE now contributes more than 50% to the maximum score (7 of 13) unlike any ASyS type, irrespective of duration, contributing a maximum of one-third to the original score. In a remarkable feat of statistical modeling, the 7 points added to the SeLECT 2.0 score achieve high statistical significance ($P < .001$) by including almost as many ASySE patients. The predictive performance of the original SeLECT score was tested in an external, multicenter cohort.[7] It found that the model can reasonably discriminate patients who did or did not develop PSE (c-statistic of 0.77) and was well-calibrated so that the absolute predicted risk corresponded with the observed risk in the validation cohort. External validation is critical to assess a predictive model's reproducibility and generalizability to novel populations. The external validation of adjusted risk prediction for PSE from a rare event like ASySE in a stroke population (0.2% in the study) requires an extremely large cohort, which likely explains its absence for the newly proposed SeLECT 2.0. This deficit, however, serves as SeLECT 2.0's Achille's heel, undermining its reliability in clinical practice compared to its predecessor. SeLECT 2.0's uncertain footing is not helped by the substantial gap between its calculated PSE risk ascribed to ASySE in the multivariable model and the unadjusted risk calculated from the 39 ASySE patient cohort, especially for the actionable 2-years follow-up period.

Nonetheless, using the strength of a large multicenter stroke cohort, the greatest contribution of the study is to show that the adage "time is brain" not only applies to stroke management but also to the duration of ASyS after stroke—the longer they are, the worse are the outcomes. The points given to the original SeLECT score predictors remain unchanged in the 2.0 version. Therefore, the former can continue to be used for predicting PSE risks in almost all patients with stroke. For the rare scenario of ASySE, the current and previous studies inform us that the risk of PSE is at least higher by 3 to 4 folds compared to shorter ASyS. The relative ease of accumulation and analysis of large-scale data today provide hope that we may soon have etiology-specific prognostic scores, including for

scenarios where the patient has a combination of short ASyS, ASySE, and electrographic seizures. In the meantime, our patients will be better served if we do not ignore ASyS after brain injuries as a benign epiphenomenon that lack impact on long-term outcomes.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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