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Strokes or Seizures? What's the Score?

Prediction of Late Seizures After Ischemic Stroke With a Novel Prognostic Model (the SeLECT Score): A Multivariable Prediction Model Development and Validation Study

Galovic M, Döhler N, Erdélyi-Canavese B, et al. *Lancet Neurol*. 2018;17(2):143-152. doi:10.1016/S1474-4422(17)30404-0 PMID: 29413315

Background: Stroke is one of the leading causes of acquired epilepsy in adults. An instrument to predict whether people are at high risk of developing poststroke seizures is not available. We aimed to develop and validate a prognostic model of late (>7 days) seizures after ischemic stroke. Methods: In this multivariable prediction model development and validation study, we developed the SeLECT score based on 5 clinical predictors in 1200 participants who had an ischemic stroke in Switzerland using backward elimination of a multivariable Cox proportional hazards model. We externally validated this score in 1169 participants from 3 independent international cohorts in Austria, Germany, and Italy and assessed its performance with the concordance statistic and calibration plots. Findings: Data were complete for 99.2% of the predictors (99.2% for Switzerland, 100% for Austria, 97% for Germany, and 99.7% for Italy) and 100% of the outcome parameters. Overall, the risk of late seizures was 4% (95% confidence interval [CI]: 4-5) 1 year after stroke and 8% (6-9) 5 years after stroke. The final model included 5 variables and was named SeLECT on the basis of the first letters of the included parameters (severity of stroke, large-artery atherosclerotic etiology, early seizures, cortical involvement, and territory of middle cerebral artery [MCA] involvement). The lowest SeLECT value (0 points) was associated with a 0.7% (95% CI: 0.4-1.0) risk of late seizures within 1 year after stroke (1.3% [95% CI: 0.7-1.8] within 5 years), whereas the highest value (9 points) predicted a 63% (42-77) risk of late seizures within 1 year (83% [62-93] within 5 years). The model had an overall concordance statistic of 0.77 (95% CI: 0.71-0.82) in the validation cohorts. Calibration plots indicated high agreement of predicted and observed outcomes. Interpretation: This easily applied instrument was shown to be a good predictor of the risk of late seizures after stroke in 3 external validation cohorts and is freely available as a smartphone app. The SeLECT score has the potential to identify individuals at high risk of seizures and is a step toward more personalized medicine. It can inform the selection of an enriched population for antiepileptogenic treatment trials and will guide the recruitment for biomarker studies of epileptogenesis.

Population-Based Assessment of the Long-Term Risk of Seizures in Survivors of Stroke

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Background and Purpose: We sought to determine the long-term risk of seizures after stroke according to age, sex, race, and stroke subtype. Methods: We performed a retrospective cohort study using administrative claims from 2 complementary patient data sets. First, we analyzed data from all emergency department visits and hospitalizations in California, Florida, and New York from 2005 to 2013. Second, we evaluated inpatient and outpatient claims from a nationally representative 5% random sample of Medicare beneficiaries. Our cohort consisted of all adults at the time of acute stroke hospitalization without a prior history of seizures. Our outcome was seizure occurring after hospital discharge for stroke. Poisson regression and demographic data were used to calculate age-, sex-, and race-standardized incidence rate ratios (IRR). Results: Among 777 276 patients in the multistate cohort, the annual incidence of seizures was 1.68% (95% confidence interval [CI]: 1.67%-1.70%) after stroke versus 0.15% (95% CI: 0.15%-0.15%) among the general population (IRR: 7.3; 95% CI: 7.3-7.4). By 8 years, the cumulative rate of any emergency department visit or hospitalization for seizure was 9.27% (95% CI: 9.16%-9.38%) after stroke versus 1.21% (95% CI: 1.21%-1.22%) in the general population. Stroke was more strongly associated with a subsequent seizure among patients <65 years of age (IRR: 12.0; 95% CI: 11.9-12.2) than in patients ≥65 years of age (IRR: 5.5; 95% CI: 5.4-5.5), and in the

multistate analysis, the association between stroke and seizure was stronger among nonwhite patients (IRR: 11.0; 95% CI: 10.8-11.2) than among white patients (IRR: 7.3; 95% CI: 7.2-7.4). Risks were especially elevated after intracerebral hemorrhage (IRR: 13.3; 95% CI: 13.0-13.6) and subarachnoid hemorrhage (IRR: 13.2; 95% CI: 12.8-13.7). Our study of Medicare beneficiaries confirmed these findings. Conclusions: Almost 10% of patients with stroke will develop seizures within a decade. Hemorrhagic stroke, nonwhite race, and younger age seem to confer the greatest risk of developing seizures.

Commentary

Stroke is a leading cause of death and disability in industrialized countries. Ischemic stroke has an overall prevalence of 2.6% in adults over 20, resulting in approximately 795,000 strokes per year. It is the fifth cause of death in the United States.[1] Stroke mortality has declined over time,[2] in part due to broader education targeting earlier symptom identification and greater awareness by the public and the health-care personnel regarding the possibility of time-sensitive treatment. In addition, improvements in interventions, allowing for longer windows of treatment, dedicated stroke units, and specialized hospital care have improved survival and outcomes. This results in a higher number of stroke survivors and with them the resulting late stroke complications, including physical and cognitive disabilities as well as poststroke epilepsy (PSE).

Seizures are a common occurrence at stroke presentation (1.53%-3%) and within the acute hospital admission (2.03%-14.6%). Seizures occurring at onset or within 7 days of stroke presentation are considered acute symptomatic seizures. Patients with cortical, extensive, or hemorrhagic strokes are thought to be at greater risk of developing acute seizures, but the risk attributable to each of these characteristics is not well established. The presence of acute poststroke seizures is associated with higher morbidity and mortality than patients with comparable strokes but no seizures.[3,4] The presence of prolonged acute seizures is also associated with the later development of PSE.[5,6]

Late seizures happen weeks to years following an acute stroke. Population cohorts with long-term follow-up described 6.4% to 11.5% of poststroke patients developed PSE with a cumulative risk over time, which continues to increase even as far as 10 years following the initial stroke.[6-8] Clinical markers of cortical involvement such as aphasia, visual neglect, or visual field cut along with stroke severity, particularly involving the MCA territory, are associated with a higher risk of PSE.

Merkler et al conducted an ambitious retrospective review which included 777,276 consecutive stroke survivor patients from 3 states over 8 years and 81,984 Medicare stroke survivors over 5 years. They found that 9.27% and 13.37%, respectively, of these patients developed PSE within 10 years. This represented a 7-fold higher risk of developing epilepsy than the general population. The authors found the highest predictors for developing seizures were: hemorrhagic stroke and having a stroke while young. In this large sample size, they were also able to describe an increased risk of PSE within the nonwhite stroke survivors, which was highest among the black population. Prior studies had identified younger age (<65) at stroke presentation as a predictor for the development of PSE.[7] These findings may be related to the presence of larger vessel strokes in the young compared to small vessel strokes seen in the older population.

Ethnic disparities in stroke risk follow a similar pattern with a higher stroke incidence among young and black population when compared to nonblacks. Death rates related to stroke are also higher in nonwhite populations.[9]

Galovic et al developed a prediction model to identify the risk of individual patients to develop PSE and validated it in 1169 patients form 3 different ischemic stroke patient cohorts. The model includes 5 variables, each one with an assigned point value which added resulted in a reliable prediction for the development of seizures over time. The SeLECT score was named after the valuables that make it: Severity of the stroke, Large artery atherosclerosis, Early seizure presentation, Cortical involvement, and MCA Territory. The model had a concordance statistic of 0.77 in validation cohorts with an excellent agreement between the predicted and observed outcomes for seizures at 1 and 5 years.

A similar score aimed to predict PSE in survivors of intracerebral hemorrhage, the CAVE score also follows the acronym of the variables considered: Cortical involvement, Age <65, Volume >10 mL, and Early seizures at presentation <7 days. Each of the variables is assigned 1 point and the summation is associated with a cumulative risk of developing PSE.[10]

Being able to identify the population at increased risk of PSE and the ability to calculate the risk specifically for each patient with stroke, open the doors for targeted patient and family education regarding the presentation, risks, and even prophylaxis for PSE, which so far has not proven efficacious in the prevention of seizures.[11] The identification of increased risk invites us to consider a discussion on seizure precipitants, seizure precautions, driving privileges, or risk of Sudden Unexpected Death in Epilepsy. It also allows us to identify a group of patients who don't have epilepsy at the moment but will likely develop it within 10 years, which is an ideal model to evaluate the efficacy of antiepileptogenic interventions.[12]

With the available information, we are equipped with the tools needed to identify poststroke patients at high risk of developing PSE. We should consider incorporating seizure presentation, possible complications, and potential treatment to the regular stroke education provided to stroke survivors and their families. The presentation of PSE will likely be in the form of focal seizures, which the patients and their families are more likely to identify as a new stroke than a seizure unless they are educated about both. Asking patients about possible

seizure symptoms in a prospective manner at follow-up visits may result in early identification and treatment of PSE. The question of performing prospective electroencephalograms (EEGs) is controversial and seen by many as a waste of resources; however, performing serial EEGs on stroke survivors was able to increase the identification of PSE to 16% of poststroke patients.[4] One more powerful argument comes to mind, cognitive deficits and depression often accompany neurologic conditions such as stroke and epilepsy. The possibility that some of these symptoms could be related to subclinical seizures and therefore could be treated and resolved is enough reason to take PSE seriously as part of stroke management and as a strategy to get our patients to live and function to their highest potential.

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