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STROKE-RELATED EPILEPSY

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Abstract: Despite significant advances in acute stroke management and reducing stroke mortality, there has been limited progress in preventing complications such as post-stroke epilepsy. PSE research is scattered worldwide, with varying methodologies and data collection. To address these challenges, we have established the International Post-Stroke Epilepsy Research Consortium (IPSEC). This protocol outlines a meta-analysis of individual patient data to determine outcomes in patients with post-stroke seizures and develop/validate prediction models for PSE, comparing them with existing models. The protocol also describes the creation of the International Post-Stroke Epilepsy Research Repository, which will support future collaborative research.[1]

Key words: Post-Stroke Epilepsy, predictors, hemorrhage, ischemia.

Cerebrovascular disease accounts for approximately 50% of epilepsies in older adults. After a stroke, some individuals' brain suffers from active epileptogenic processes, eventually leading to seizures.[2–4] Post-stroke epilepsy (PSE) is associated with increased morbidity, including cognitive decline, dependence and poor quality of life, and is a critical determinant factor of stroke prognosis.[5] Unfortunately, no proven antiepileptogenesis drugs are available to inhibit the post-stroke epileptogenic process.[3] Because the research related to PSE is scattered worldwide, there is a critical need to integrate these efforts. We, therefore, founded an International Post-stroke Epilepsy Research Consortium (IPSERC). We will collect the following patient outcomes: seizure frequency, severity (e.g., impairment of awareness (yes/no), bilateral tonic-clonic seizures (yes/no), occurrence or frequency of status epilepticus and hospitalization); other aspects of outcome, such as patient-reported quality of life, cognitive function, side effects of treatment, response to anti-seizure medication, independence, mood (depression/anxiety), and economic costs; Modified Rankin Scale (mRS) scores; causes of death; National Institutes of Health Stroke Scale (NIHSS); Glasgow Coma Scale (GCS), home time, and length of hospitalization. Although the existing and previous datasets may not include epilepsy outcomes, we will ask collaborators to collect these data in the prospective study sample. The investigators will provide de-identified patient data on validated predictors of PSE. We will collect the following predictor/modifier variable data from individual studies:

- Stroke subtype (ischemic, hemorrhagic)

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- Stroke mechanism

- Stroke location

- Date of the first patient stroke

- Date of subsequent patient stroke

- Demographic characteristics (age, sex, race, body mass index)

- Systolic and diastolic blood pressure

- Vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, myocardial infarction, atrial fibrillation, peripheral arterial disease, heart failure with reduced ejection fraction, previous stroke, smoking, alcohol, other recreational drugs)

- History of depression, anxiety, and dementia

- Comorbidities (chronic liver disease, chronic kidney disease, malignancy)

- Antithrombotic medications

- Antihypertensive medications

- Statin use

- Presence of seizure

- Seizure subtype

- Recurrent seizures

- Time to first seizure onset after stroke

- Anti-seizure medications Follow-up duration, laboratory investigations (including glucose, HbA1c, haemoglobin, white blood cell count, platelets, international normalized ratio, lipid profile, blood urea nitrogen, creatinine, estimated glomerular filtration rate, sodium, potassium, C-reactive protein, and procalcitonin), acute infection data, cognitive impairment data, imaging data, electroencephalography (EEG) data, tissue plasminogen activator (tPA) eligibility for endovascular treatment, tPA treatment data, endovascular therapy data, haemorrhagic transformation, any surgery performed, superficial siderosis, microbleeds, intracerebral haemorrhage (ICH) score, infarct volume, haematoma volume, intraventricular extension, midline shift, herniation, and hydrocephalus. Data are presented as *n* (%) prevalence or mean ± SD. Meta-analyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat; Englewood, NJ, USA) and a *P* value <0.05 was considered statistically significant. A random effects model was used to calculate the pooled estimates of incidence and risk factors, and 95% confidence intervals (CIs), and was used to account for heterogeneity between studies, assessed using the statistic. Meta-analyses of the

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pooled incidence rate and 95% CIs for post-stroke ES and PSE were conducted, and the findings were displayed using forest plots. Pooled odds ratios (ORs) and 95% CIs were calculated for the risk factors of post-stroke ES and PSE, including age, stroke type, severity of stroke (based on NIHSS), cortical involvement, territories affected, hemorrhagic transformation, post-stroke ES, and alcohol use. For the risk factor of age, there was variability in the age groupings used by individual studies included in the meta-analysis. For the present study, different age groupings were collapsed and patients aged < 65 years were compared with those aged ≥ 65 years. Similarly, for stroke severity, the definitions of NIHSS categories varied between different studies, so patients were dichotomized for comparison into those with NIHSS score > 15 and those with NIHSS score ≤ 15. For the territories affected, total anterior circulation infarction and partial anterior circulation infarction were combined as anterior circulation infarct. Subgroup analyses of the incidence and risk factors of post-stroke ES and PSE were conducted in children (aged <18 years) and adults (aged ≥18 years). In adults, the risk of post-stroke ES was higher in those with hemorrhagic stroke compared with ischemic stroke, more severe stroke, cortical involvement, and hemorrhagic transformation . In adults, the risk of PSE was higher in those with more severe stroke, those with hemorrhagic stroke compared with ischemic stroke, those with anterior circulation infarcts compared with posterior circulation infarcts, those with cortical involvement versus without cortical involvement, those with hemorrhagic transformation versus without hemorrhagic transformation, and those with post-stroke ES versus without post-stroke ES.

In children, the risk of PSE was higher in those with cortical involvement than without cortical involvement. The present meta-analysis assessed the incidence of post-stroke ES and PSE using a large number of studies from multiple countries, including North America, Europe, Asia, and Africa, which enhanced the generalizability of study findings. Overall, the rate of PSE was found to be higher than the rate of post-stroke ES, and rates of ES and PSE were higher in children than in adults. Risk factors for post-stroke ES included hemorrhagic strokes, severe stroke, cortical involvement, and hemorrhagic transformation, while risk factors for PSE included stroke severity, anterior circulation infarcts, cortical involvement, hemorrhagic transformation, and the presence of ES. Older age and alcohol misuse were not found to be associated with increased risk of post-stroke ES or PSE.

The present systematic review improves on previously published reviews by using definitions of ES and PSE that are consistent with ILAE guidelines, by including more studies in the analysis, and analyzing risk factors, such as age, stroke territories, and whether post-stroke ES were associated with PSE, and by conducting subgroup analyses of incidence and risk factors in adults and children. A prior meta-analysis identified 32 studies reporting the incidence of post-stroke ES (0.04), late seizures (LS: 0.05) and PSE (0.05)[2]. In the present systematic review, many more studies reporting on the incidence of PSE were identified, and the incidences of post-stroke ES and PSE were higher than those reported by the previous study[4].There is huge variability in the reported incidence of ES, LS, and PSE in individual studies, which may be related to the population studied, methodology, country, and type and extent of stroke, with a higher incidence in hemorrhagic stroke than ischemic stroke[13]. The risk of ES is greatest in the first 24 h after stroke[7]. The risk of PSE is highest in the 6–12 months following a stroke [7] and 84% of those who develop PSE do so within the first 2 years after a stroke[8]In the present study, a more detailed timing of ES or PSE was not considered. Previous meta-analyses have evaluated the risk factors for different

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categories of post-stroke seizures and PSE. For example, a previous study evaluating the risk factors of PSE, in which PSE was defined as seizures occurring more than 7 days after stroke, found that cortical involvement, hemorrhagic stroke, and ES were risk factors for PSE[9].An evaluation of risk factors for ES (i.e., seizures occurring less than 7 days after stroke) and LS (i.e., seizures occurring more than 7 days after stroke), reported that hemorrhagic stroke, hemorrhagic transformation of infarct, severe stroke, and alcoholism were associated with increased risk of ES, while cortical involvement and severe stroke were associated with PSE[9]The present study identified further risk factors for both ES and PSE compared with the previous meta-analyses a hemorrhagic stroke was not identified as a risk factor for PSE. Differences in findings may be related to combined primary hemorrhage and hemorrhagic transformation of ischemic stroke in their definition of hemorrhagic stroke. Hemorrhagic transformation was found to be associated with increased risk for ES and PSE in the present analyses. Hemorrhagic transformation may result in the ischemic penumbra tissue becoming more excitable[14] and this, along with the increased irritability caused by blood degradation products on cortical neurons, may predispose individuals to developing post-stroke seizures. However, hemorrhagic transformation of acute ischemic stroke has been shown to be associated with increased risk of ES and PSE. In addition, ES was found to be higher among those with symptomatic hemorrhagic transformation, but not among those with asymptomatic hemorrhagic transformation.

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