

**Journal Club: The risk of new-onset epilepsy and refractory epilepsy in older adult stroke survivors**

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## Background and significance

The incidence of stroke increases with age and stroke is a significant cause of new-onset epilepsy in the elderly.<sup>1</sup> A few small studies previously suggested that older epilepsy patients and those with post-stroke epilepsy tend to respond to anti-epileptic drug (AED) treatment and are less likely to become refractory,<sup>2,3</sup> but this relationship is under-investigated.

In this Journal Club article<sup>4</sup>, Burneo *et al.* conducted a large cohort study in Ontario, Canada, confirming this relationship. Moreover, they showed that most of the deaths in those with post-stroke epilepsy were unrelated to stroke or epilepsy.

## Hypothesis and design

Given the lack of studies of adequate design (i.e. many were case-control studies) or sufficient size, the authors' main aim was to more reliably determine the incidence and factors associated with post-stroke epilepsy at older ages and its long-term prognosis. Although not expressly stated, the implied hypothesis was that age is protective of post-stroke epilepsy and refractory post-stroke epilepsy, in accordance with previous studies.

This has important implications for healthcare service planning (for example to facilitate appropriate investigation and clinical care of these patients), patient counselling with regards to future risk of epilepsy and addresses interesting pathophysiological questions.

The study was a large retrospective cohort study using multiple linked administrative datasets from the universal health care system in Ontario, Canada.

## Methods

### *Case identification*

The authors used the Ontario Stroke Registry to identify stroke patients, discharged from one of 12 stroke centres for the first event between 2003 and 2009. An initial cohort of 42,172 patients was identified. Stroke subtypes included hemorrhagic, ischemic or 'other' (including TIAs and unspecified).

The largest exclusion criteria was a missing or invalid health card number. Study-specific exclusions included those younger than 67 years, with acute symptomatic seizures or death prior to discharge, seizures in the preceding 10 years (determined by validated ICD-9/10 codes), AED use in the preceding 2 years or brain tumour/ epilepsy surgery.

### *Outcome identification*

Patients were administratively followed for 2 years after discharge to assess for post-stroke epilepsy. A pre-defined algorithm identified cases hospitalized for epilepsy or connected to  $\geq 3$  physician billings for seizures/ epilepsy, 30 days apart. Refractory epilepsy was operationally defined as not responding to two AED intervention trials within 18 months.

MRI brain and EEG was considered adequate investigation for seizures, in line with published standards for investigation of new-onset seizures.

A state mortality registry was used to determine the 5-year case-fatality for those with post-stroke epilepsy. Relevant ICD-9 codes were used to identify cause-specific deaths, which included: stroke-related, epilepsy-related, and all-cause.

#### *Factors associated with post-stroke epilepsy*

Covariates used in the model were chosen from the literature as those previously shown to affect long-term outcomes following stroke due to the small number of patients identified with refractory post-stroke epilepsy. These included stroke type, age, sex, thrombolysis receipt, anticoagulant medication receipt, and stroke severity.

Different datasets of Ontario's universal health care system were linked with the main dataset to identify the above covariates of interest (see paper for details<sup>4</sup>).

#### *Statistical analysis*

Simple statistics were used to assess for baseline differences in those with and without post-stroke epilepsy. Missing data was accounted for by multiple imputation prior to multivariable analysis.

The risk of developing post-stroke epilepsy and refractory post-stroke epilepsy was calculated using 2 Fine and Gray competing risk regression models (accounting for the risk of death).

Multivariable analysis including predefined covariates was performed to assess the factors associated with post-stroke epilepsy and refractory epilepsy.

### **Results**

From the initial cohort, 23,034 patients (54.6%) were excluded creating a final study population of 19,138. Of these, 210 (1.1%) developed epilepsy within 2 years; 24 (11.4%) were assessed with EEG and 19 (9.0%) with MRI brain. During an average follow-up of 3.9 years, 27 (12.9%) post-stroke epilepsy patients became refractory.

Post-stroke epilepsy was associated several variables including younger age, higher Charlson Comorbidity Index and a greater prevalence of depression, but only younger age and acute treatment with thrombolysis were independent predictors in the pre-specified multivariate model. By contrast, predictors for refractory post-stroke epilepsy included younger age and female sex. Interestingly, the initially significant independent effects of anti-coagulation and high Canadian Neurologic Scale score both diminished over the course of follow-up.

The 210 post-stroke epilepsy patients had an all-cause 5-year mortality rate of 46.2%, of who 13 (6.2%) died of stroke-related causes. No patients died of epilepsy-related causes.

### **Interpretation**

This study by Burneo *et al.* has contributed to the literature by reinforcing previously suggested trends of age-related protection from post-stroke epilepsy. The strengths include its large, clearly defined population and use of validated registry-based methods to capture multiple covariates and mortality.

The main limitation, common to many registry-based studies, pertains to potential biases with incomplete capture of all cases and outcomes resulting in possible underestimation of the incidence of post-stroke epilepsy at older ages.

#### *Case ascertainment*

Case selection bias might contribute to under-ascertainment of patients with high risk of post-stroke epilepsy.

Firstly, although the study has a clearly defined population, in a strict epidemiological sense it is a multicenter hospital-based study. “Ideal” population-based studies use multiple overlapping methods of case ascertainment to identify patients from primary and secondary care records to capture those with out-of-area or inpatient strokes, who may be some of the frailest patients with a high risk of post-stroke epilepsy.<sup>5</sup>

Secondly, over half the initial cohort was excluded, including 3,573 patients with missing or invalid health card numbers. These are likely to include those with low socioeconomic status and a plausibly higher risk of post-stroke epilepsy.<sup>6,7</sup>

Thirdly, patients with prior AED use were excluded from the study as a surrogate marker of pre-existing epilepsy. However, the coding would not have distinguished patients prescribed AEDs for alternative diagnoses, such as severe depression or neuropathic pain. Exclusion of these patients could also result in underestimation of post-stroke epilepsy risk, given the known associations of depression and epilepsy,<sup>6</sup> similarly demonstrated in this study.

Finally, patients with seizures prior to discharge were excluded, but it is known there are two peaks in post-stroke seizure/epilepsy occurrence on the first day and 6–12 months after a stroke.<sup>7,8</sup>

In addition to potential selection bias, lack of information or information bias in relation to the stroke subtypes can also limit the interpretation of the study results.

For example, all subtypes of stroke and TIA were included but no sensitivity analyses were performed, despite the higher risk of post-stroke epilepsy in those with intracerebral hemorrhage.<sup>8,9</sup> Whether the identified trends are driven by one subtype in particular is not known as the proportional representation of different stroke subtypes, including those ‘unable to determine’, is not reported.

#### *Outcome ascertainment*

Under-ascertainment of the outcome would also influence the apparent low risk of post-stroke epilepsy at older ages.

The authors identified cases of post-stroke epilepsy using a previously validated algorithm, but with a sensitivity of only 73.7%. Reasons for this, and whether there could be any systematic bias, are not explored in the paper but one might argue that increasing age is likely to be associated with “false-negative” cases, for example minor seizures could be easily missed or ignored in those living in nursing homes. Other possible explanations for the low sensitivity include uncomprehensive codes, and out-of-area events.

### *Predictors*

The authors have provided some explanations as to their remarkable finding that age appears protective for post-stroke epilepsy. However, alternative explanations include the potential biases we have outlined leading to lower outcome ascertainment.

Moreover, in the multivariate model, the authors have not explained how the covariates 'interaction between anticoagulant medication receipt and time' and 'stroke severity and time' were chosen; it seems likely this was a data-driven post-hoc analysis.

### *Long-term mortality*

The authors found a very low risk of stroke-related death and no patients died of epilepsy-related causes. However, it is unknown whether all relevant ICD mortality codes were used, for example capturing cases of Sudden Unexpected Death in Epilepsy (SUDEP), which could be coded as sudden cardiac death. Yet, there is unlikely to be any systematic bias here since it is plausible there is an increased chance of deaths being attributed to stroke or epilepsy with a relevant history, but the authors in fact found the opposite trend.

### *Investigations proposed for post-stroke epilepsy*

The authors' standard of investigation of post-stroke epilepsy was based on general guidelines for new-onset seizures and, unsurprisingly, they report low compliance in this cohort. In our experience, EEG in particular is unlikely to be management-changing in this context and the authors have not provided any commentary on why they feel this a clinically relevant work-up for an elderly post-stroke epilepsy patient.

In conclusion, despite the large study population, given the lack of granularity in stroke subtyping, the exclusion of large numbers of patients with potential for systematic bias, the results would be difficult to translate to clinical practice. Similarly, they highlight an under-investigation of post-stroke epilepsy patients, but do not make the case that their standard is clinically meaningful.

Nevertheless, the study has made an important contribution to the field and highlighted significant trends that should be explored in future prospective studies.

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