

## EPILEPSY AS A WARNING SIGN FOR STROKE

### Late-onset Seizures as a Predictor of Subsequent Stroke

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**BACKGROUND:** Cerebrovascular disease is thought to be a major cause of epilepsy in late life. We investigated the hypothesis that the onset of seizures after the age of 60 years in people with no history of overt stroke might be associated with an increased risk of subsequent stroke.

**METHODS:** Data were obtained from the U.K. General Practice Research Database on 4,709 individuals who had seizures beginning at or after the age of 60 years, and on 4,709 randomly selected controls with no history of seizures, matched for age, sex, and general practice. Individuals with a history of cerebrovascular disease, other acquired brain injury, brain tumor, drug or alcohol misuse, or dementia were not eligible for inclusion. Computerized

patients' records were searched for subsequent diagnoses of stroke.

**RESULTS:** Log-rank testing, adjusted for matching, showed a highly significant difference in stroke-free survival between the two groups ( $P < 0.0001$ ). With a Cox's model, we estimated that the relative hazard of stroke at any point for people with seizures compared with the control group was 2.89 (95% Confidence Interval [CI], 2.45 to 3.41).

**CONCLUSIONS:** Our findings show that the onset of seizures in late life is associated with a striking increase in the risk of stroke. Further research is warranted to assess the benefit of specific interventions to prevent stroke in patients with seizures.

### COMMENTARY

The cost of treating stroke in the United States is estimated at \$30 million per year. In a Canadian study, the direct costs related to care of 285 patients with stroke was \$6.6 million over a period of 2 years (1). Thus if just one stroke can be prevented, it means significant savings for the society as well as for the individual patient. Recent research on the prevention of stroke has focused on controlling risk factors, such as cholesterol, cardiac disease, smoking, hypertension, diabetes, and weight control. Early warning signs are crucial to the prevention of a stroke or, at least, to limiting its size and consequences. Therefore given findings such as those presented by Cleary and colleagues, which indicate that seizures are warning signs for stroke in the elderly, seizures should probably be added to the list of risk factors.

The study by Cleary et al. is unique because it is the first report to focus on epilepsy as a warning signal of impending stroke. Most literature has reported on the prevalence and incidence of epilepsy after stroke. Clinicians know that stroke is associated with an increased risk of developing epilepsy. In this study, Cleary et al. used the General Practice Research Database (GPRD) at the U.K. Office of National Statistics and identified 4,709 patients older than 60 years, with new-onset epilepsy or first-ever antiepileptic drug (AED) prescription plus epilepsy, and 4,709 normal controls older than 60 years, without epilepsy or AED use. The investigators found that epilepsy

onset later in life carries with it a threefold risk of subsequent stroke.

However, some problems are inherent in the analysis of the patients in the database and in the inclusion criteria. Although patients with known cerebrovascular disease were excluded from the study, it is impossible to tell whether the epilepsy patients actually had prior minor lacunar stroke that was not identified on computerized tomography (CT). Surely most of the patients were not subjected to modern magnetic resonance imaging (MRI) studies to detect small bleeds and infarctions (2). Additionally, radiologic studies may have been inaccurate or not advanced enough to detect small strokes that could have caused the seizure. Of course, the trouble with retrospective case record studies is that they can be inaccurate. As the authors pointed out, it is not certain that all of the seizures were actually seizures; some of the events identified as seizures could have been transient ischemic attacks (TIAs). The opposite also is true—some events identified as TIAs may have actually have been seizures. It also would have been interesting to know whether the patients had any of the risk factors for stroke, such as hypertension (2), and how many, if any, were being treated with aspirin at the time of the first seizure. It is not possible to answer these questions, as patients were not accessed individually but rather as a group. In spite of the problems inherent in this study, the important point is that older patients, with new-seizure

onset that is without a known cause, should be treated in the same manner as a patient who has had a TIA.

A next step for future research would be to perform a randomized study with patients who have had a seizure for no apparent reason and who have been evaluated by MRI to assure that the seizure was not caused by hemorrhage. The study design might include one group treated only with AEDs and a second group treated with both AEDs and low-dose aspirin. It also might be feasible to use body weight (or body mass index [BMI]) to estimate the likelihood of increased cerebrovascular risk from diabetes, hypertension, and hyperlipidemia (3). This is the triad of metabolic syndromes among overweight older people that commonly predispose this patient group to stroke. Did the patients having epilepsy before stroke have these risk factors? Were they overweight? The authors did not provide answers to these clinically important questions. Another area for future research would be to investigate whether some of the AEDs might have provoked or protected against stroke. Although this hypothesis sounds far fetched, it is not totally implausible. Finally, the implications of the study by Cleary et al. for clinical care are so important that their analysis should be replicated in a population in another geographic area to determine whether this “epilepsy signal” of increased risk is reliable and can be generalized.

As the authors conclude, important take-home messages exist. Both new-onset epilepsy and just one seizure event must be taken seriously in the elderly, and cerebrovascular evalua-

tions should be included in patient workups to find predictors of stroke, such as hypertension, cardiac arrhythmias, diabetes, hypercholesterolemia, and homocystinemia. An evaluation for a seizure must include MRIs and not just CT scans, as CT can miss small strokes or hemorrhages (4). Consider that epilepsy patients might need treatment not just with AEDs but also with other drugs, such as angiotensin-converting enzyme (ACE) inhibitors, statins, and aspirin.

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## References

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