



Modifiable Risk Factors of Dementia in Older Adults With Epilepsy: An Opportunity to Flatten the Curve?

A Nationwide, Retrospective, Data-Linkage, Cohort Study of Epilepsy and Incident Dementia

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Objective: To determine the association of epilepsy with incident dementia by conducting a nationwide, retrospective data-linkage, cohort study to examine whether the association varies according to dementia subtypes and to investigate whether risk factors modify the association. **Methods:** We used linked health data from hospitalization, mortality records, and primary care consultations to follow up 563 151 Welsh residents from their 60th birthday to estimate dementia rate and associated risk factors. Dementia, epilepsy, and covariates (medication, smoking, comorbid conditions) were classified with the use of previously validated code lists. We studied rate of dementia and dementia subtypes in people with epilepsy (PWE) and without epilepsy using (stratified) Kaplan-Meier plots and flexible parametric survival models. **Results:** PWE had a 2.5 (95% confidence interval [CI] 2.3-2.6) times higher hazard of incident dementia, a 1.6 (95% CI 1.4-1.8) times higher hazard of incident Alzheimer disease (AD), and a 3.1 (95% CI 2.8-3.4) times higher hazard of incident vascular dementia (VaD). A history of stroke modified the increased incidence in PWE. PWE who were first diagnosed at ≤ 25 years of age had a dementia rate similar to that of those diagnosed later in life. PWE who had ever been prescribed sodium valproate compared to those who had not were at higher risk of dementia (hazard ratio [HR] 1.6, 99% CI 1.4-1.9) and VaD (HR 1.7, 99% CI 1.4-2.1) but not AD (HR 1.2, 99% CI 0.9-1.5). **Conclusion:** PWE compared to those without epilepsy have an increased dementia risk.

Commentary

The risk of critical cognitive decline in people with epilepsy (PWE) is not a novel, 21st-century concept. In his classical 1881 textbook, Gowers describes that the “greater imperfections of intellectual power” is “much dreaded, and is often most serious” consequence of epilepsy.¹ However, only in the last couple of years, some remarkable studies have highlighted that the “imperfections of intellectual power” can present as frank dementia in older adults with chronic epilepsy.² These recent findings were presaged in the 1990s by few population-based studies suggesting increased dementia risk in PWE. With PWE living healthier and longer lives than ever, we again need to look to large population-based studies, not just to confirm the evidence of increased dementia risk in older PWE but also to provide early signals of means to flatten the curve of the coming dementia epidemic. Herein lies the importance of the study by Schnier et al from Wales, United Kingdom.³

This retrospective cohort study’s primary aim is to compare the dementia incidence risk in the older PWE and non-epilepsy population. It used the national health care database that accounts for around 80% Welsh population. The authors analyzed 563,151 residents from their 60th birthday to the

diagnosis of dementia, death, or end of follow-up in June 2018. During a median follow-up of 10 years, older PWE were at a 2.5 times higher hazard of dementia diagnosis. Among PWE with follow-up available for 21 and 25 years after their 60th birthday, 20% and 40% were diagnosed with dementia, respectively. The study’s unique value is the information it provides on the incidence hazard of the 2 most common dementia subtypes, Alzheimer’s dementia (AD) and vascular dementia (VaD), along with the investigation of the impact of some mitigating factors on this association. People with epilepsy had a 1.6 times higher hazard of AD diagnosis and a 3.1 times higher hazard for VaD. Adjusting the survival model individually for exposure to smoking, diabetes, hypertension, alcohol use, head injury history, and socioeconomic deprivation did not change the hazard of dementia incidence in PWE. However, a notable exception was controlling for stroke history, which substantially reduced the hazard of dementia and VaD incidence in PWE. Comparing PWE with early-onset (≤ 25 years of age) epilepsy to the rest, the authors did not find an association of epilepsy duration on dementia incidence. Interestingly, just 67% of the 19,150 PWE were exposed to 1 or more anti-seizure medications (ASMs). Only exposure to



sodium valproate was associated with a higher hazard of dementia and VaD incidence, 1.6 and 1.7 times, respectively, which remained significantly high even after adjustment for sex, stroke history, and bipolar disease.

There are several limitations of the study, including its lack of generalizability across racially diverse PWE population. The potential modifiers of dementia investigated are limited by the study's dependence on variables collected in a national administrative database. Additionally, clinical diagnosis of dementia subtypes is challenging. The risk of misclassification is high, particularly the easy labeling of VaD in people with stroke history, even if the cognitive decline is AD-related or a mixed subtype. These issues may partially explain the reduction in hazard of dementia and VaD incidence after controlling for stroke history, which, nonetheless, remains twice as high for PWE than people without epilepsy. Shining a light on VaD's contribution to the dementia burden in older PWE is a remarkable contribution of this large, population-based study. Vascular dementia accounted for close to one-third of the total dementia incidence in the study cohort and was substantially higher in older PWE. Controlling individual, potentially modifiable, cerebrovascular risk factors did not affect the hazard ratio of dementia in PWE, likely because these factors work in combination to mediate the dementia risk, akin to the causation of stroke. The work of Schnier et al helps us conjure the possibilities of potentially modifiable dementia risk factors in PWE.

According to estimates, complete elimination of potentially modifiable dementia risk factors would reduce the dementia incidence burden by 35%.⁴ These include midlife (age 45–65 years) factors such as hypertension, obesity, hearing loss, and later life (age > 65 years) factors such as smoking, diabetes, depression, physical inactivity, and social isolation. PWE commonly suffer depression, physical inactivity, and social isolation,^{5,6} but the effect of these factors on their cognition remains poorly investigated. The rest of the abovementioned potentially modifiable risk factors primarily pertain to cerebrovascular health and in combination with findings from Schnier et al raises questions about the triangulated pathophysiology underlying epilepsy, AD, and VaD that increases dementia incidence in older PWE.

The bidirectionality of epilepsy and dementia has received notable attention recently.² In contrast, the stroke and epilepsy relationship is usually considered a one-way street, moving from the former to the latter. However, recent studies challenge this notion by showing that older PWE suffer increased cerebrovascular disease burden. A 45-year long follow-up study of childhood-onset epilepsy patients found a 2.5 times higher rate of cerebrovascular disease marker in the form of white matter hyperintensities (leukoaraiosis) on 3T magnetic resonance imaging (MRI) compared to controls.⁷ Strikingly, this difference was noted despite PWE and the controls having a similar biochemical and clinical profile of cerebrovascular risk factors.⁷ These findings raise the possibility that epilepsy itself, including its underlying etiology, interictal epileptiform discharges, seizures, and ASMs can predispose PWE to increased

cerebrovascular disease burden. But, does the markers of elevated cerebrovascular disease in PWE contribute to cognitive decline? A recent study in older adults (age ≥ 55 years) with temporal lobe epilepsy found that after controlling epilepsy-related clinical variables, leukoaraiosis on MRI remained significantly associated with poorer memory performance.⁸ A definitive evidence for advocating aggressive management of cerebrovascular and lifestyle risk factors to prevent dementia in older PWE is beyond our immediate scientific horizon. However, the emerging evidence in epilepsy research and the extrapolation from dementia literature suggests that our patients will be better served by us taking a proactive stance in managing the modifiable dementia risk factors, in addition to improved seizure control.

The study by Schnier et al lacks information on indication, dose, and duration of ASM use for seizure control. Nonetheless, the association of valproate use with increased dementia incidence in PWE is worthy of further investigation. Valproate is known to be associated with increased obesity and metabolic syndrome risk,⁹ two factors that were not controlled for in the reviewed study but are known to promote cerebrovascular disease. Enzyme-inducing ASMs substantially increase cerebrovascular disease risk¹⁰ as well, and insurance database research from the United States reveals a worrisome trend of growing prescription of such ASMs to the older PWE.¹¹ Hopefully, future research in conjunction with on-going studies translating the preclinical findings of improved cognition with newer ASMs,^{2,12} will inform us if judicious ASM use could be a modifiable dementia risk factor in PWE or ASMs themselves will become dementia-modifying therapies.

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