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Epilepsy, Cardiovascular Risks, and Dementia: A Ménage à Trois

Association of Dementia Risk With Focal Epilepsy and Modifiable Cardiovascular Risk Factors

Tai XY, Torzillo E, Lyall DM, Manohar S, Husain M, Sen A. *JAMA Neurol*. 2023;80(5): 445-454. doi:10.1001/JAMANEUROL.2023.0339. PMID: 36972059, PMCID: PMC10043806.

Importance: Epilepsy has been associated with cognitive impairment and potentially dementia in older individuals. However, the extent to which epilepsy may increase dementia risk, how this compares with other neurological conditions, and how modifiable cardiovascular risk factors may affect this risk remain unclear. Objective: To compare the differential risks of subsequent dementia for focal epilepsy compared with stroke and migraine as well as healthy controls, stratified by cardiovascular risk. Design, setting, and participants: This cross-sectional study is based on data from the UK Biobank, a population-based cohort of more than 500 000 participants aged 38 to 72 years who underwent physiological measurements and cognitive testing and provided biological samples at 1 of 22 centers across the United Kingdom. Participants were eligible for this study if they were without dementia at baseline and had clinical data pertaining to a history of focal epilepsy, stroke, or migraine. The baseline assessment was performed from 2006 to 2010, and participants were followed up until 2021. Exposures: Mutually exclusive groups of participants with epilepsy, stroke, and migraine at baseline assessment and controls (who had none of these conditions). Individuals were divided into low, moderate, or high cardiovascular risk groups based on factors that included waist to hip ratio, history of hypertension, hypercholesterolemia, diabetes, and smoking pack-years. Main outcomes and measures: Incident all-cause dementia; measures of executive function; and brain total hippocampal, gray matter, and white matter hyperintensity volumes. Results: Of 495 149 participants (225 481 [45.5%] men; mean [SD] age, 57.5 [8.1] years), 3864 had a diagnosis of focal epilepsy only, 6397 had a history of stroke only, and 14 518 had migraine only. Executive function was comparable between participants with epilepsy and stroke and worse than the control and migraine group. Focal epilepsy was associated with a higher risk of developing dementia (hazard ratio [HR], 4.02; 95%CI, 3.45 to 4.68; $P < .001$), compared with stroke (HR, 2.56; 95%CI, 2.28 to 2.87; $P < .001$), or migraine (HR, 1.02; 95% CI, 0.85 to 1.21; $P = .94$). Participants with focal epilepsy and high cardiovascular risk were more than 13 times more likely to develop dementia (HR, 13.66; 95%CI, 10.61 to 17.60; $P < .001$) compared with controls with low cardiovascular risk. The imaging subsample included 42 353 participants. Focal epilepsy was associated with lower hippocampal volume (mean difference, −0.17; 95%CI, −0.02 to −0.32; $t = -2.18$; $P = .03$) and lower total gray matter volume (mean difference, −0.33; 95%CI, −0.18 to −0.48; $t = -4.29$; $P < .001$) compared with controls. There was no significant difference in white matter hyperintensity volume (mean difference, 0.10; 95%CI, −0.07 to 0.26; $t = 1.14$; $P = .26$). Conclusions and relevance: In this study, focal epilepsy was associated with a significant risk of developing dementia, to a greater extent than stroke, which was magnified substantially in individuals with high cardiovascular risk. Further findings suggest that targeting modifiable cardiovascular risk factors may be an effective intervention to reduce dementia risk in individuals with epilepsy.

Commentary

The concept of "epileptic dementia" and the controversy of whether the co-occurrence of epilepsy and dementia is merely coincidental or whether one disease truly increase the risk of the other is centuries old.[1] While this controversy remains unresolved, the strong association between epilepsy and dementia has become increasingly evident. Studies have suggested a substantially elevated risk of dementia in people with epilepsy (PWE).[2-4] Similarly, the link between cardiovascular risks and dementia is uncontroversial.[4] However, the relative weight of epilepsy compared to other neurologic disorders and how cardiovascular risks impact dementia risk in PWE are not well-established. It is this ménage à trois of epilepsy, dementia, and cardiovascular risks that the study by Tai et al attempts to understand using a UK-based database.[5]

The authors included 494 149 individuals without prior history of dementia in the UK Biobank Cohort to investigate the risk of incident dementia in focal epilepsy compared to stroke, migraine, and healthy controls. All-cause dementia and focal epilepsy were identified using International Classification of Diseases (ICD) codes. Cox proportional hazard regression models were used with incident all-cause dementia as the primary outcome. All analyses were adjusted for age, sex, education, socioeconomic status, and cardiovascular risks. Mutually exclusive groups of different neurological disorders and controls were included. At baseline, 0.78% had focal epilepsy, 1.3% had stroke, and 2.93% had migraine. Cardiovascular risk was calculated using a previously developed score[6] based on hypertension, hyperlipidemia, diabetes, waist-to-hip ratio, smoking pack-years, and APOEe4 allele status. Low, moderate, and high cardiovascular risks were present in 27.1%, 55.4%, and 17.5% of individuals, respectively. People with epilepsy had lower executive function compared to controls and migraine but comparable to those with stroke. Epilepsy was associated with a higher risk of dementia (adjusted hazard ratio [HR] = 4.020) compared to stroke (HR = 2.56) and migraine (HR = 1.02). Dementia risk was comparable in early and late-onset epilepsy (LOE). Epilepsy was associated with a higher risk of dementia compared to stroke in those with moderate and high cardiovascular risks. The cumulative effect of epilepsy and cardiovascular risk factors was large; PWE with high cardiovascular risk had a 13.66-fold risk of dementia compared to controls with low cardiovascular risks. Sensitivity analysis assessed dementia risk, in epilepsy and stroke, stratified by cardiovascular risks with and without APOEe4. After excluding the APOEe4 genotype from the risk score, PWE with high cardiovascular risk had an HR of 7.53 compared to those with no epilepsy and low cardiovascular risk. To account for anti-seizure medications (ASMs), the number of ASMs was included in the subgroup analysis. More ASMs were associated with lower executive function but not with a higher incidence of dementia. In neuroimaging analysis, epilepsy was associated with lower hippocampal (−0.17) and total gray matter volume (−0.33) but not with white matter hyperintensity (WMH) volume.

The strengths of the study lie in its large sample size, a large epilepsy cohort with longitudinal follow-up, and robust statistical analyses. Few large-scale studies have controlled such an analysis for cardiovascular risks.[3,4] In contrast to Tai et al, in a large Welsh database, a limited number of cardiovascular risks did not impact the HR of dementia in PWE.[3] The current study is distinctive in that, instead of individual risks, it utilizes risk scores and stratifies the analysis accordingly. Another strength is the inclusion of APOEe4 status in the risk score, which is the single most common and independent genetic predictor of both LOE and dementia and, rightfully, deserves attention.[7,8]

Another point of long-standing contention is whether it is epilepsy or ASMs that contribute to dementia. Without a doubt, the confounding effect of ASM is an important consideration when assessing cognition in PWE. The authors accounted for this by comparing cognition with the ASM number in PWE and those without epilepsy taking ASMs. However, the relationship between some ASMs with cognitive decline may be more significant than others.[3] A study of 563 151 individuals demonstrated that valproate was associated with a higher incidence of dementia and vascular dementia (VaD), and lamotrigine with a higher incidence of Alzheimer disease (AD) in PWE.[3] In a population-based study, prolonged ASM use (>1 year) and use of higher ASM doses were associated with significantly higher dementia risk in PWE.[9] Therefore, further studies on the dose, duration, or type of ASMs are needed to better understand the impact of ASMs on cognition.

A meta-analysis of 42 studies with 1027 PWE and 1122 controls showed significantly prevalent widespread WMH in focal epilepsy.[10] Yet another study with 5 decades of follow-up noted significant WMH in 245 PWE compared to controls.[11] Thus, it has been proposed that epilepsy in itself may contribute to WMH which may represent relevant biological substrates underlying cognitive decline in PWE.[10,12] Surprisingly, Tai et al did not find a difference in WMH in those with and without epilepsy. However, the findings of reduced hippocampal and gray matter volume in PWE by the authors are consistent with existing literature. In fact, hippocampal atrophy is a known biomarker of both PWE and AD and may explain the predisposition for dementia in PWE.[13] However, the correlation between neuroimaging findings and dementia development is worthy of further attention in future studies.

Seizure burden, disease duration, and seizure frequency are known predictors of dementia in PWE.[3,4,14] However, given the nature of a broad-based database, epilepsy-specific information (epileptogenic zone, etiology, types/frequency/severity of seizures, degree of epilepsy control, and the presence of hippocampal sclerosis) could not be assessed in the current study.

Epilepsy is thought to have more intimate ties with VaD (HR = 3.1) and AD (HR = 1.6) compared to other dementia subtypes.[3,4] It has been suggested that temporal lobe epilepsy (TLE) and AD may have a shared pathological basis, including hippocampal network alterations and tau accumulation.[13] Tau accumulation correlates with the degree of cognitive impairment in both AD and TLE without AD.[13] Similarly, cerebrovascular risks are more closely linked to VaD than other dementia subtypes.[4] Therefore, it may be argued that the authors perhaps took a simplistic view by analyzing all-cause dementia with no investigation into dementia subtypes.

Given the observational nature of the current study, causality cannot be established. Authors utilized ICD codes for diagnosis, which carry a risk of misdiagnosis and may not be accurate. Electroencephalogram findings were not considered. UK biobank represents generally healthy adults; therefore, results may not be generalizable. The rigor of cognitive testing also remains a question of concern and so does the lack of consideration for the extent of cognitive decline. Furthermore, in the absence of Kaplans-Meier curves, it is difficult to ascertain whether the cognitive reserve of PWE was comparable to healthy controls at baseline. If PWE had lower cognitive

reserve at baseline, then earlier cognitive decline is an expected outcome.

Finally, the age-old conundrum of "The Chicken or the Egg" paradox, the bidirectional link between epilepsy and dementia,[13] raises the query of which one causes the other.[4] The authors attempted to mitigate the potential for reverse causality by assessing dementia risk at different follow-ups (10 and 5-14 years). However, the possibility of undetected dementia and reverse causality may still be there since epilepsy from neurodegeneration may become evident >10 years before the clinical manifestations of dementia.[15] This unanswered question is deserving of more attention in future studies.

The current study adds to the growing evidence that PWE is more likely to develop dementia and that this risk is substantially magnified in the presence of cardiovascular risks. Early screening and targeted interventions toward modifiable cardiovascular risks may offer effective prevention strategies and an "opportunity to flatten the curve"[12] in delaying dementia onset in the aging population of PWE.

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Declaration of Conflicting Interests

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