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Epilepsy and Neurodegeneration: A Bidirectional Relationship

The Bi-Directional Association Between Epilepsy and Dementia. The Framingham Heart Study

Stefanidou M, Beiser AS, Himali JJ, et al. *Neurology*. 2020. doi:10.1212/WNL.0000000000011077.

Objectives: To assess the risk of incident epilepsy among participants with prevalent dementia, and the risk of incident dementia among participants with prevalent epilepsy in the Framingham Heart Study (FHS). Methods: We analyzed prospectively collected data in the Original and Offspring FHS cohorts. To determine the risk of developing epilepsy among participants with dementia and the risk of developing dementia among participants with epilepsy we used separate, nested, case–control designs, and matched each case to 3 age-, sex-, and FHS cohort-matched controls. We used Cox proportional hazards regression analysis, adjusting for sex and age. In secondary analysis, we investigated the role of education level and apolipoprotein $\varepsilon 4$ allele status in modifying the association between epilepsy and dementia. Results: A total of 4906 participants had information on epilepsy and dementia and dementia follow-up after age 65. Among 660 participants with dementia and 1980 dementia-free controls there were 58 incident epilepsy cases during follow-up. Analysis comparing epilepsy risk among dementia cases versus controls yielded (hazards ratio [HR] = 1.82 [95% CI:1.05-3.16], $P = .034$). Among 43 participants with epilepsy and 129 epilepsy-free controls, there were 51 incident dementia cases. Analysis comparing dementia risk among epilepsy cases versus controls yielded (HR = 1.99 [1.11-3.57], $P = .021$). In this group, among participants with any post-high school education, prevalent epilepsy was associated with a nearly 5-fold risk for developing dementia (HR = 4.67 [1.82-12.01], $P = .001$) compared to controls of the same educational attainment. Conclusions: There is a bidirectional association between epilepsy and dementia with either condition carrying a nearly 2-fold risk of developing the other when compared with controls.

Dementia in Late Onset Epilepsy: The Atherosclerosis Risk in Communities Study

Johnson EL, Krauss GL, Kucharska-Newton A, et al. *Neurology*. 2020.

Objective: To determine the risk of dementia after the development of late-onset epilepsy (LOE). Methods: We used data from the Atherosclerosis Risk in Communities (ARIC) cohort study, which started in 1987 to 1989 with 15 792 mostly black and white men and women from 4 US communities. We identified LOE (seizures starting at age 67 or later) from linked Medicare claims data. We used a Cox proportional hazards regression model to evaluate associations between LOE and dementia through 2017 as ascertained from neuropsychological testing, interviews, and hospital discharge surveillance; and we used multinomial logistic regression to assess the risk of dementia and mild cognitive impairment in the subset with full neuropsychological assessments available. We adjusted for demographics, and vascular and Alzheimer disease risk factors. Results: Of 9033 ARIC participants with sufficient Medicare coverage data (4980 [55.1%] female, 1993 [22.1%] black), 671 met the definition of LOE. 279 (41.6%) participants with LOE and 1408 (16.8%) without LOE developed dementia ($P < .001$). After a diagnosis of LOE, the adjusted hazard ratio for developing subsequent dementia was 3.05 (95% CI: 2.65-3.51). The median time to dementia ascertainment after the onset of LOE was 3.66 years (Q1-Q3 1.28-8.28 years). Interpretation: The risk of incident dementia is substantially elevated in individuals with LOE. Further work is needed to explore causes for the increased risk of dementia in this growing population.

Commentary

The relationship between epilepsy and memory complaints has been widely accepted in the fields of epilepsy and neuropsychology. In fact, $\sim 50\%$ of patients with epilepsy report cognitive deficit(s) as one of their most troublesome epilepsy-related symptoms.[3] Although in young patients with

epilepsy these symptoms are unlikely to be related to underlying and/or ongoing neurodegeneration, the chances of neurodegeneration as a cause of or a contributor to cognitive decline increase with age. The increasing incidence and prevalence of epilepsy in the elderly compounded by ageing of the population suggest that cognitive complaints and decline in patients with epilepsy may soon become a major problem in the clinical practice.[4,5] The epidemiological studies show gradually increasing risk of developing epilepsy with age. The highest epilepsy rates observed in septuagenarians and older groups are mostly attributed to higher incidence and prevalence with age of strokes, head traumas, brain tumors, and, of interest here, neurodegenerative disorders including dementia. In fact, dementia has been reported to increase the risk of subsequent seizures and epilepsy at least 6-fold in an older epidemiological study where participants with dementia were matched to not demented individuals by age, sex, and duration of follow-up.[5] However, the question of the relationship between dementia and epilepsy remains.

This is where 2 recent studies come into play. The first study tests bidirectional relationships between epilepsy and dementia,[1] while the second study tests the risk of developing dementia after being diagnosed with late-onset epilepsy (LOE).[2] These prospective data collections use different methodologies and the initial impetus for conducting these studies was different. The study by Stefanidou et al is based on the longitudinal data collected continuously since 1948 in a mostly white population in Framingham, Massachusetts (Framingham Heart Study; FHS).[1] In contrast to the FHS, the Johnson et al study draws its longitudinal data from the Atherosclerosis Risk in Communities (ARIC) study initiated in 1987 in 4 communities in Maryland, North Carolina, Minnesota, and Mississippi. This study includes 20% blacks and 80% whites (data on other races/ethnicities were collected but numbers were too small to report).[2] There are, of course, other differences between the studies. In the FHS, screening for dementia (including examinations) and for epilepsy were not initiated at study inception but rather later depending on whether this was the first or the second generation of enrollees, and the design was nested case control (participants and matched controls were extracted from a larger dataset at a 1:3 rate). In the ARIC study, the results of in-person cognitive screening were later linked with Medicare claims epilepsy/seizure data. Despite apparent differences in populations studied and their approaches, the results of the studies are similar. In the FHS, the risk for developing epilepsy in already demented individuals was 1.82 while the risk of developing dementia in already diagnosed with epilepsy participants was 1.99; the risk of dementia was higher in participants with higher level of education (high-school vs higher than high-school education) and estimated at 4.67. The ARIC study estimated the risk of developing dementia in LOE to be 3.05. Of importance, both studies controlled for multiple confounders and analyzed the contributions of the apolipoprotein $\varepsilon 4$ (APOE4) status. No significant relationships between epilepsy and any of age, sex, or APOE4 in their effect on incident dementia were found in the FHS, and no interactions between race, sex, or the APOE4 genotype and the effect of LOE on the risk of dementia were identified in the ARIC study.

This brings us to 2 main questions: what is the commonality (or commonalities) that can explain the bidirectional relationship of epilepsy and dementia and what are the challenges for the future for the clinicians and researchers alike?

The answer to the first question is gradually emerging from animal and human studies. Although the process of epileptogenesis in dementia is not completely elucidated, animal research links excessive deposition of amyloid in the hippocampus to hyperexcitability and eventual neuronal loss, impaired synaptic plasticity, remodeling of normal circuits, and development of interictal and ictal electroencephalogram changes that may precede declines in memory. In addition to amyloid deposits, tau protein has been shown to exert indirect (modulatory) and direct (pro-epileptic) toxicity in, for example, mouse model of dementia.[6] However, more important is the translation of these animal findings to human evidence. Since there is commonality between epilepsy and dementia in that temporal lobes are frequently involved in both, human studies have focused on examining neuropathology and imaging of temporal lobes. In neuropathological studies, high percentage of autopsy-confirmed Alzheimer disease (AD) samples also have epilepsy and the prevalence of epilepsy in AD is 13.4% in one study.[7] In one sample of 50- to 65-year-old epilepsy patients who received anterior temporal lobectomy, 94% showed hyperphosphorylated tau pathology and 12% of the studied cohort had Braak staging III/IV compared to 8% in nonepilepsy population; the more widespread and pronounced the tau pathology was, the greater was the cognitive decline one year after surgery.[8] Other commonalities between AD and other dementias and epilepsy exist that can potentially explain their bidirectional relationship. However, these relationships which include, for example, the presence/absence of neuroinflammation,[9,10] the differential contributions of controlled versus uncontrolled seizures to cognitive decline and the contribution of specific medications are not discussed here.

The second question is regarding the challenges that are facing clinicians and researchers. Although research into the relationship between epilepsy and dementia continues to focus on amyloid, tau, neuroinflammation, or other factors and common pathways that are contributing to both, epilepsy clinicians are left to wonder what to tell their patients with epilepsy when they ask, for example, "What is epilepsy? Do I have AD?" or "I have memory problems . . . Am I developing AD . . . ?" Although the answers are not simple and straightforward, we need to discuss these issues with our patients—preferably before these symptoms set in. Should we preemptively discuss with our new-onset epilepsy patients that they are likely to develop cognitive issues and that epilepsy may, through some common pathway, evolve into or be associated with symptoms of dementia? We do this already for sudden unexplained death in epilepsy (SUDEP) in initial discussion with the patient and their family, so should it be the same for AD/dementia? Or, should we wait until the patient asks? The answer to these questions is not very simple and may be situation depended. Another question is whether we should be

developing and implementing pharmacological and nonpharmacological interventions to delay or abort the process of cognitive decline and potential development of dementia in our patients—the answer to this is "yes" as such efforts are already ongoing and efficacy of some of them has been reported.[11-13] Finally, the question of anti-seizure medication selection may come into play because of the recent report of carbamazepine and oxcarbazepine having anticholinergic effects that could potentially accelerate development or progression of cognitive deficits,[14] while other anti-seizure medications such as levetiracetam are currently under investigation for the treatment of cognitive impairments (eg, NCT03489044 or NCT03875638).

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