ARTICLE

Bi-directional association between epilepsy and dementia

The Framingham Heart Study

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Abstract

Objective

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 *APOE* ε4 allele status in modifying the association between epilepsy and dementia.

Results

A total of 4,906 participants had information on epilepsy and dementia and dementia follow-up after age 65. Among 660 participants with dementia and 1,980 dementia-free controls, there were 58 incident epilepsy cases during follow-up. Analysis comparing epilepsy risk among dementia cases vs controls yielded a hazard ratio (HR) of 1.82 (95% confidence interval 1.05–3.16, $p = 0.034$). Among 43 participants with epilepsy and 129 epilepsy-free controls, there were 51 incident dementia cases. Analysis comparing dementia risk among epilepsy cases vs controls yielded a HR of 1.99 (1.11–3.57, $p = 0.021$). 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], $p = 0.001$) compared to controls of the same educational attainment.

Conclusions

There is a bi-directional association between epilepsy and dementia. with either condition carrying a nearly 2-fold risk of developing the other when compared to controls.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer dementia; **AED** = antiepileptic drug; **CI** = confidence interval; **DLB** = dementia with Lewy bodies; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **FHS** = Framingham Heart Study; **FTD** = frontotemporal dementia; **HR** = hazard ratio; **ICD-9** = International Classification of Diseases–9; **TBI** = traumatic brain injury; **VaD** = vascular dementia.

Dementia affects approximately 47 million people worldwide,[1] a number that is expected to double within 20 years. Epilepsy affects approximately 45.9 million people[2] and, like dementia, its incidence increases with age. The highest incidence of new epilepsy cases is among those over the age of 65.[3,4] Epilepsy in older age is often attributed to acquired cerebral insults such as strokes, dementia, tumors, and head injury.[5,6] There is emerging evidence of a bi-directional association between dementia, particularly Alzheimer dementia (AD), and epilepsy based on observations that support an overlap in patterns of neuronal degeneration in the hippocampal circuitry[7] that may account for progressive worsening of cognition and memory in both conditions. Previous studies show a 2- to 10-fold increased risk of seizures among patients with dementia[8–11] and one registry-based study showed an increased risk of dementia[12] among patients with epilepsy. The role of epileptogenesis, either as the underlying culprit or as a consequence of neurodegeneration, remains unclear. Given the aging of the population, with those above 65 estimated to reach 1 billion worldwide by 2030,[13] understanding the epidemiologic link between these 2 common conditions is of great public health importance.

We assessed the incidence of both dementia and epilepsy in the Framingham Heart Study (FHS), a large, population-based cohort, to determine the influence of each condition on the risk of developing the other and assess potential modifying factors. FHS offers prospective surveillance of dementia and we performed rigorous review of available study and medical records to retrospectively identify epilepsy cases.

Methods

Study population

The FHS is an ongoing longitudinal, community-based study that began in 1948 with the enrollment of 5,209 participants into the original cohort (Gen 1)[14] to prospectively investigate risk factors for cardiovascular disease. In 1971, the offspring of the original cohort and their spouses (n = 5,124) were enrolled in the offspring cohort (Gen 2).[15] Prospective, longitudinal surveillance of Gen 1 and Gen 2 participants is based on examination visits that occur every 2 and 4 years, respectively.

Adjudication of epilepsy and dementia cases

The FHS administers surveillance questions/forms at each examination visit, but it also has access to medical records of outpatient, inpatient, and emergency department visits. In order to identify epilepsy cases, a broad screen for patients with potential epilepsy or seizures was performed in Gen 1 and 2 cohorts across all examinations using (1) routine chart review for any neurologic condition that is performed as part of the stroke and dementia substudies of the FHS or history of conditions with a high risk of seizures (traumatic brain injury [TBI] and cerebral tumors), (2) self-report of seizures or syncope on the standard questionnaire given at each examination visit, (3) ICD-9 codes associated with epilepsy, myoclonus, convulsions/seizures, syncope, or loss of awareness (345.00–345.91, 780.39, 779.0, 333.2, 780.02, 780.2, and 780.31), and (4) antiepileptic drug (AED) use reported at study visits. The charts of the identified participants were reviewed in detail and we abstracted information on the semiology of the event of interest, brain imaging, EEG, cardiac, or other available relevant data using an epilepsy screening form. Following consensus review by 2 epileptologists (MS, OD and/or DF), cases were adjudicated into (1) definite, (2) probable, or (3) suspected epilepsy; (4) single definite/probable/suspected unprovoked seizure; (5) acute symptomatic seizure; (6) not epilepsy or seizure; or (7) cases with insufficient data to reach a conclusive diagnosis based on the definitions of epilepsy proposed by the International League Against Epilepsy Commission on Epidemiology[16] (table 1). Epilepsy cases for the present study included cases that met criteria for categories 1–4. In sensitivity analysis, we also looked at the association between epilepsy and dementia excluding suspected epilepsy/seizure cases. Surveillance for dementia is ongoing at FHS and decisions on dementia diagnosis and subtype are made at a consensus review with the presence of a cognitive neurologist and a neuropsychologist that considers FHS neurologists' examinations, family interviews, and brain autopsy data.[17] Dementia cases satisfy DSM-IV criteria.[18] Systematic cognitive evaluation in the FHS started at examination 17 (1981–1984) and examination 5 (1991–1995) in Gen 1 and Gen 2, respectively. Similarly, a screening question regarding the occurrence of a seizure was first introduced at examination 21 (1988–1992) in Gen 1 and at examination 5 in Gen 2.

We used a nested case-control design to investigate incident epilepsy following dementia diagnosis. Each dementia case was matched at the year of dementia diagnosis (match year) to 3 controls from the same FHS cohort (Gen 1 or Gen 2) and same sex, who were free of dementia at match year and aged within 2 years of the age of the corresponding case. Epilepsy follow-up was through 2016, with epilepsy cases followed to year of epilepsy diagnosis and controls followed to year last known epilepsy-free.

Table 1 Epilepsy definitions

Definite epilepsy	Probable epilepsy	Suspected epilepsy	Other outcomes
Evidence of recurrent unprovoked seizures and documentation of diagnosis by neurologist/epileptologist	Lack of documented diagnosis by a specialist, but evidence of seizures with one or more of the following: • Remote neurologic injury preceding onset of seizures such as stroke, hemorrhage, trauma, and supportive clinical information including brain imaging (CT or MRI) demonstrating structural brain lesion • Brain tumor: either primary or metastatic to brain • History of seizures in a first-degree relative • History of meningitis or documented encephalitis • Cerebral palsy • EEG report describing epileptiform abnormalities • Use of antiepileptic medications	Available evidence suggests a diagnosis of epilepsy but documentation of seizures or supportive information is not available	• Definite, probable, and suspected single unprovoked seizure • Acute symptomatic seizures • Not epilepsy • Cases with insufficient data to reach a conclusion

We used a similar process to select the sample for the incident dementia following epilepsy analyses. Each epilepsy case was matched at the year of epilepsy diagnosis (match year) to 3 controls from the same FHS cohort (Gen 1 or Gen 2) and same sex, who were free of epilepsy at match year and aged within 2 years of the age of the corresponding case. Dementia cases were followed to year of dementia diagnosis and controls had available dementia follow-up to at least age 65 and were followed to year last known dementia-free.

We used Cox proportional hazards regression to compare epilepsy cases to epilepsy–free controls with respect to incident dementia, and to compare dementia cases to dementia-free controls with respect to incident epilepsy, adjusting for sex and age at matching. Secondary models additionally adjusted for education and presence of the *APOE* ε4 allele (*APOE4*), and we used models with interaction terms to investigate effect modification by age, sex, *APOE4*, and educational attainment.

Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Standard protocol approvals, registrations, and patient consents

All protocols were approved by the Boston University Medical Center institutional review board. All participants provide written informed consent when joining the FHS.

Data availability

All data collected on FHS participants, including those used in our analysis, are available to qualified scientific investigators outside FHS who complete a research application, in accordance to FHS data sharing policies.

Results

A total of 4,906 participants in Gen 1 and Gen 2 had FHS examination follow-up at minimum until age 65 and information on both epilepsy and dementia after their respective entry dates. Among these 4,906 participants, there were 888 dementia cases (815 with available screening for incident epilepsy after the date of dementia diagnosis) and 90 epilepsy cases (43 with available screening for incident dementia that extended beyond the age of 65).

Epilepsy risk among participants with prevalent dementia

Among the 815 patients with dementia who had epilepsy follow-up after their dementia diagnosis, 3 sex-, age-, and cohort-matched controls were available for each of 660 dementia cases (78% with AD type, including mixed-type, 10% dementia with Lewy bodies [DLB], 5% vascular dementia [VaD] without AD, 1% frontotemporal dementia [FTD], and 6% other) for a total of 2,640 participants. There were 58 incident epilepsy cases during follow-up, 19 (2.9%) among those with prevalent dementia, and 39 (2.0%) among the dementia-free controls (table 2). Cox proportional hazards model comparing epilepsy risk among patients with dementia vs controls yielded a hazard ratio (HR) of 1.82 (95% confidence interval [CI] 1.05–3.16, $p = 0.034$).

Additional adjustment for education (HR 1.88 [1.08–3.27], $p = 0.026$) or for *APOE4* (HR 1.96 [1.08–3.58], $p = 0.028$) yielded similar results. No significant interactions were noted between prevalent dementia and any of age, sex, *APOE4*, or level of education in their effect on incident epilepsy. Exclusion of participants with dementia and prevalent stroke and their controls showed a slightly increased risk of subsequent epilepsy (578 dementia cases and 1734 controls, HR 2.30 [1.28–4.15], $p = 0.006$).

Dementia risk among participants with prevalent epilepsy

Each of the 43 patients with epilepsy who had available cognitive assessment after their epilepsy diagnosis was matched to 3 epilepsy-free controls on sex, age, and cohort, for a total of 172 participants. There were 51 incident dementia cases

Table 2 Demographics, educational level, *APOE4* status, available follow-up, and incident epilepsy cases among participants with dementia and their controls

	Dementia cases	Dementia-free controls
N	660	1,980
Male	227 (34)	681 (34)
Age, y	83 ± 7	83 ± 7
Any college	253 (40)	795 (41)
No college	382 (60)	1,142 (59)
APOE4	174/543 (32)	332/1,658 (20)
Follow-up period, y	4 (1–19)	5 (1–21)
Incident epilepsy cases	19 (2.9)	39 (2.0)

Abbreviations: *APOE4* = *APOE* ε4 allele (genetic data were available in a subgroup of participants).
Values are n (%), mean ± SD, or median (range).

during follow-up (84% with AD type), 18 (41.9%) among patients with epilepsy and 33 (25.6%) among the epilepsy-free controls (table 3). Cox proportional hazards model comparing epilepsy cases to controls with respect to incident dementia yielded an HR of 1.99 (1.11–3.57, $p = 0.021$). Additional adjustment for education (HR 2.00 [1.10–3.62], $p = 0.023$) or for *APOE4* (HR 2.32 [1.27–4.24], $p = 0.007$) yielded similar results. No significant interactions were noted between prevalent epilepsy and any of age, sex, or *APOE4* in their effect on incident dementia. Sensitivity analysis limited to epilepsy cases of unknown cause (excluding prevalent stroke, TBI, and brain tumor) yielded similar results (31 epilepsy cases and 93 controls, HR 2.02 [1.06–3.85], $p = 0.033$).

We found a significant interaction between prevalent epilepsy and education in their effect on incident dementia. Due to the relatively small numbers of events, we combined levels of education to create just 2 levels of education for the stratified analysis. Nearly half of the participants (n = 80) had no education beyond high school and we used this cut point to stratify our analyses (interaction $p = 0.043$). Among the 80 participants who had no education beyond high school, 29 developed dementia, and prevalent epilepsy did not significantly increase the risk of subsequent dementia (HR 1.10 [0.49–2.50], $p = 0.812$) compared to epilepsy-free controls. Among the 90 participants with any post–high school education, 22 developed dementia, and prevalent epilepsy was associated with a nearly 5-fold risk for developing dementia (HR 4.67 [1.82–12.01], $p = 0.001$) compared to controls of the same educational attainment.

In additional analysis, when we used a stricter definition of epilepsy excluding suspected epilepsy and suspected single unprovoked seizures, the association between epilepsy and subsequent dementia (29 definite and probable epilepsy cases and their 87 controls) showed an identical effect size, but with a wider confidence interval (HR 1.99 [0.90–4.43], $p = 0.091$). The same was true among participants with prevalent dementia when we censored out the 18 incident suspected epilepsy/seizure cases (HR 1.82 [0.94–3.53], $p = 0.077$).

Discussion

Our study provides strong evidence from a large, population-based, prospective cohort that epilepsy and dementia are interlinked and patients have a 2-fold risk of developing either condition in the presence of the other.

Epileptic seizures are more common in patients with dementia; 2- to 10-fold increased risk has been reported in AD,[8–10] which accounts for 60%–70% of all dementias, but seizures are also seen in VaD,[9] DLB,[8] dementia associated with Down syndrome,[19] and FTD.[8] Worsening dementia has been linked to higher risk of seizures, but duration of dementia and age at dementia onset have yielded conflicting data.[9,10,20,21] Our findings support a nearly 2-fold risk of developing epilepsy following dementia diagnosis (primarily of the AD type), which lies on the lower end of prior observations. The proportion of patients with AD who have had at least one unprovoked seizure varies between 1.5% and 64% in different prospective and retrospective hospital-based studies.[19] Two studies comparing incident rates of seizures in AD vs control populations calculated a nearly 10-fold higher risk.[8,22] A population-based study in Rochester, Minnesota, reported an odds ratio of 6.2 (95% CI 2.2–17) for first unprovoked seizure among patients with AD compared to controls.[11] The lower rates observed in our study may reflect differences in epilepsy/seizure case adjudication methods, study design, surveillance of dementia methods, and racial

Table 3 Demographics, educational level, *APOE4* status, available follow-up, and incident dementia cases among participants with epilepsy and their controls

	Epilepsy cases	Epilepsy-free controls
N	43	129
Male	14 (33)	42 (33)
Age, y	76 ± 10	76 ± 10
Any college	22 (51)	68 (54)
No college	21 (49)	59 (46)
APOE4	9/38 (24)	29/120 (24)
Follow-up period, y	4 (1–19)	5 (1–21)
Incident dementia cases	18 (42)	33 (26)

Abbreviations: *APOE4* = *APOE* ε4 allele (genetic data were available in a subgroup of participants).
Values are n (%), mean ± SD, or median (range).

makeup between the different study populations. The FHS participants are mostly Caucasian, but a higher rate of late-onset seizures has been found among Black patients.[23]

The exact mechanism that drives epileptogenesis in dementia is not fully defined. In mice, excessive β-amyloid (Aβ) peptide deposition is linked to hippocampal neuronal loss and hyperexcitability,[24] impaired synaptic plasticity,[25] and generation of interictal epileptiform activity that may precede memory decline.[24] In humans, direct amyloid epileptogenicity is supported by observations of very high risk for seizures among patients with early-onset AD secondary to autosomal dominant mutations in amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*) and, to a lesser degree, presenilin 2 (*PSEN2*).[19] The *APOE4* allele has also been linked to late-onset epilepsy, even in individuals without dementia,[19,26] as well as in posttraumatic epilepsy.[27] In addition to the modulation effect tau protein exerts on amyloid excitotoxicity, there appears to be a direct proepileptic tau toxicity, as seizures are also seen in tauopathies that lack amyloid deposition (FTD). Hyperphosphorylated tau deposition has also been implicated in both posttraumatic and refractory epilepsy.[28,29]

Although the risk of seizures in dementia has been widely studied, very few epidemiologic studies have reported on the risk of dementia among patients with epilepsy. In one study based on Dutch morbidity registries, history of epilepsy was shown to carry a moderate risk for development of dementia (relative risk, 1.5; 95% CI 1.4–1.7) over an 8-year follow-up period.[12] This result is similar to the 2-fold increased risk observed in this study, but the interaction with education level is reported for the first time. Among participants with higher education, risk for incident dementia was nearly 5-fold among those with epilepsy compared to controls of the same educational level. Data from the Rotterdam Study showed that AD prevalence was higher among participants with lower education, despite adjustment for cardiovascular disease, and the authors argued that early dementia may be missed in highly educated individuals despite rigorous testing.[30] A recent study by Horvath et al.[31] showed that among 42 patients with AD who underwent continuous EEG, higher education was associated with increased risk of comorbid seizures, a finding that may be associated with more advanced disease at the time of dementia diagnosis among the highly educated. One possible explanation for our findings is that patients with higher education levels have a high degree of AD or other neurodegenerative pathology before showing obvious cognitive symptoms; this highly epileptogenic pathology leads to seizures before clinical dementia. Further studies with larger samples that will allow for comparisons of additional educational attainment levels will be needed to examine the dose effect of education on dementia risk among patients with epilepsy.

There is growing evidence that epilepsy, even subclinical, may coexist in certain individuals in the early stages of dementia[13,32–34] and accelerate the dementing process, especially executive function.[35,36] In a retrospective, case–control study that examined the prevalence of adult-onset, cryptogenic seizures predating the clinical manifestation of AD, it was found that seizures begin on average 4.6 years prior to the onset of cognitive symptoms and cognitive decline starts 3.6 years earlier compared to those who have AD without seizures.[37] There is also some evidence to suggest that this deleterious effect may be partially reversible by certain AEDs, namely levetiracetam, which was associated with improved cognitive performance in patients with AD and seizures compared to lamotrigine and phenobarbital, despite similar seizure control.[38] Cryptogenic, well-controlled, late-onset epilepsy has also been linked to increased $A\beta_{1\text{-}42}$ concentration in CSF and higher risk for development of AD in a prospective study with 3-year follow-up,[39] but the presence of pathologic amyloid did not invariably predict the progression to dementia.

Our study is one of few large, prospective, population-based studies to demonstrate a bi-directional link between dementia and epilepsy. We used a rigorous method of defining new-onset epilepsy cases that excludes acute symptomatic seizures (in the setting of sepsis, hypoglycemia, hypertensive urgency, anoxia, or acute stroke), which are believed to be a consequence of acute metabolic disturbances, as well as other mimics of seizures. Based on this rigorous epilepsy case adjudication, we, a priori, decided to include both suspected cases and single unprovoked seizures in the analysis, the latter as a marker of intrinsic epileptogenicity, as we wanted our sample of participants to better reflect the actual burden of disease in the specific population. Sensitivity analysis following exclusion of suspected cases, as mentioned above, showed an identical risk to that seen in our primary model in both directions of association, though the smaller number of cases led to a wider CI.

When investigating the association between epilepsy and dementia, one possible confounder is the presence of a clinical stroke, as cerebrovascular insults are well-established risk factors for both conditions.[23,40] In our study, among the participants with epilepsy and their controls there were only 10 prevalent strokes. Conversely, despite a larger number of prevalent strokes among participants with dementia and their controls, only 3 had incident epilepsy. Therefore, we were not able to complete further mediation analysis, but sensitivity analysis excluding participants with dementia and prevalent stroke showed similar results, as noted above. Another limitation of our study is that we have not accounted for possible antiepileptic drug effect on the diagnosis of dementia. A recent study from Finland showed a consistent upward trend of AED use with increasing age among elderly with and without AD.[41] Prior studies have shown association between AED use and dementia,[42,43] but a causative link has not been proven,[44–46] despite reported negative cognitive effects for some of these agents.[47] Possible confounders include the underlying indication for the AED use, which may instead be the determinant of dementia,[43] or that some of these indications may actually reflect symptoms of early dementia (seizures, anxiety, depression, insomnia).[48] Preliminary data

adjusting for history of use of old vs new-generation AEDs vs no AED use among our patients with epilepsy failed to show any significant interactions, but given the fact that we have not measured variables relating to dose and duration of treatment, this effect will require further investigation. Detailed seizure frequency, which has been linked to worse cognitive outcomes in refractory epilepsy,[49] was not collected in our epilepsy cases and, therefore, we were not able to assess whether there is an effect of seizure burden on the positive association noted between epilepsy and subsequent dementia. Finally, the FHS focuses on a primarily Caucasian population, which limits applicability of our results to other populations.

Understanding the epidemiology of epilepsy and dementia can help shape health care policies and reduce the burden of disease[50]; the FHS, with its wealth of prospectively collected cerebrovascular risk factor, imaging, neuroinflammation, and genetic data, is among the best suited cohorts to further try to disentangle the association seen between these 2 prevalent conditions in older age.

Data in the FHS show a 2-fold risk of developing dementia among those with prevalent epilepsy. Furthermore, among participants with post–high school education who have epilepsy, this risk becomes 5-fold when compared to controls of the same, higher educational level. Further studies are needed to define whether there is a bi-directional causative association between these 2 entities or if shared underlying pathophysiologic mechanisms cause both.

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Disclosure

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