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Relative Incidence of Seizures and Myoclonus in Alzheimer's Disease, Dementia with Lewy Bodies, and Frontotemporal Dementia

Alexander J. Beagle[1,*], **Sonja M. Darwish**[1,*], **Kamalini G. Ranasinghe**[1], **Alice L. La**[1], **Elissaios Karageorgiou**[1,2], and **Keith A. Vossel**[1,3]

[1]Memory and Aging Center, Department of Neurology, University of California, San Francisco, USA.

[2]Neurological Institute of Athens, Athens, Greece.

[3]N. Bud Grossman Center for Memory Research and Care, Institute for Translational Neuroscience, and Department of Neurology, University of Minnesota, Minneapolis, MN, USA.

Abstract

Background—Patients with Alzheimer's disease (AD) are more prone to seizures and myoclonus, but relative risk of these symptoms among other dementia types is unknown.

Objective—To determine incidence of seizures and myoclonus in the three most common neurodegenerative dementias: AD, dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD).

Methods—Our institution's medical records were reviewed for new-onset unprovoked seizures and myoclonus in patients meeting criteria for AD (n=1,320), DLB (n=178), and FTD (n=348). Cumulative probabilities of developing seizures and myoclonus were compared between diagnostic groups, whereas age-stratified incidence rates were determined relative to control populations.

Results—The cumulative probability of developing seizures after disease onset was 11.5% overall, highest in AD (13.4%) and DLB (14.7%) and lowest in FTD (3.0%). The cumulative probability of developing myoclonus was 42.1% overall, highest in DLB (58.1%). The seizure incidence rates, relative to control populations, were nearly 10 fold in AD and DLB, and 6 fold in FTD. Relative seizure rates increased with earlier age-at-onset in AD (age <50, 127 fold; 50–69, 21 fold; 70+, 2 fold) and FTD (age <50, 53 fold; 50–69, 9 fold), and relative myoclonus rates

Correspondence should be addressed to Keith A. Vossel; kvossel@umn.edu.

*Authors contributed equally

AUTHOR CONTRIBUTIONS

AJB and SMD contributed equally to this study and were involved with study design, data collection, analysis, interpretation, and manuscript preparation. KGR contributed to study design, analysis, interpretation, and manuscript preparation. AL contributed to data collection and manuscript preparation. EK contributed to analysis, interpretation, and manuscript preparation. KAV conceptualized the study and contributed to design, data collection, analysis, interpretation, and manuscript preparation. All authors have reviewed and approve of the final draft of this manuscript.

COMPETING INTERESTS

The authors have no conflict of interest to report.

increased with earlier age-at-onset in all groups. Seizures began an average of 3.9 years after the onset of cognitive or motor decline, and myoclonus began 5.4 years after onset.

Conclusions—Seizures and myoclonus occur with greater incidence in patients with AD, DLB, and FTD than in the general population, but rates vary with diagnosis, suggesting varied pathomechanisms of network hyperexcitability. Patients often experience these symptoms early in disease, suggesting hyperexcitability could be an important target for interventions.

Keywords

Alzheimer's disease; dementia with Lewy bodies; epilepsy; frontotemporal dementia

INTRODUCTION

Neurodegenerative disease represents a major cause of seizures in older adults. Seizures are known to occur more frequently in patients with Alzheimer's disease (AD) than in the general population, despite widely varied estimates [1–3]. Emerging evidence suggests that seizures can accompany AD in earlier stages than previously recognized [4, 5]. Seizures in AD can escape detection because they are often non-motor in nature [6, 7]. Additionally, subclinical epileptiform activity, the occurrence of epileptiform activity in the absence of seizures, can be detected in over 40% of AD patients when they undergo extended neurophysiological monitoring [8]. Both seizures and subclinical epileptiform activity in AD are associated with accelerated cognitive decline [8–10], a phenomenon that could relate to increased amyloid-beta (Aβ) and tau production due to periodic increases in synaptic activity [11–13] as well as chronic compensatory remodeling of neuronal circuits [14, 15]. Previous studies suggest that seizures and myoclonus, which are both signs of network hyperexcitability, could predict shortened survival in AD [16, 17].

Network hyperexcitability in AD has been attributed to aberrant network activity within disease-specific circuits induced by amyloid precursor protein (APP) and its metabolites, most notably Aβ [18]. Recent investigation implicates disease proteins that are not unique to AD in the propagation of aberrant network excitability, such as microtubule-associated protein tau, present in both AD and frontotemporal dementia (FTD) pathology, and α-synuclein, which is associated with Parkinson's disease (PD) and dementia with Lewy bodies (DLB) [18, 19]. Selective expression of tau containing four repeats in the repeat domain, which is the predominant tau isoform that aggregates in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), worsens functional outcome in mice compared to three-repeat tau, possibly through increases in network excitability [20]. Overexpression of tau with mutations linked to FTD or the A152T variant, which is linked to several tauopathies, also increases seizure susceptibility in transgenic mice [21, 22]. Additionally, apolipoprotein E4, the most common risk factor for AD, contributes to network hyperexcitability in animal models by causing tau-dependent decrease in GABAergic interneurons in the hippocampus [23]. Finally, overexpression of α-synuclein is sufficient to cause aberrant network excitability in experimental models of DLB, AD, and comorbidity [24].

The occurrence of network hyperexcitability in dementia has also been explored from the perspective of calbindin-D_{28K} levels, which are reduced in brain regions where chronic over-excitation occurs. Overexpression of APP/Aβ and α-synuclein have each been associated with a reduction in calbindin in the hippocampi of transgenic animal models, and similar changes are observed in postmortem brain samples from patients with AD and DLB [18, 24].

These animal studies strongly implicate numerous disease proteins in the generation of network hyperexcitability in dementia. The relative contribution of each protein and their potential interrelationships remain unknown. Furthermore, the incidence of epileptic activity in patients with non-AD forms of dementia has not yet been analyzed in depth. The rate at which patients with non-AD dementia develop seizures has been suggested to be lower than the rate in AD [25], but the comparison of seizure occurrence has not gone beyond this level of distinction. Our knowledge of the relative rates and timing of onset of myoclonus between dementias is also limited.

Here, we examined the incidence of network hyperexcitability in the forms of seizures and myoclonus in the three most common forms of degenerative dementia syndromes, AD, FTD, and DLB. Comparisons were also conducted between clinical subtypes of each dementia group, including DLB and concurrent AD (DLB-AD) and FTD-spectrum disorders including behavioral variant frontotemporal dementia (bvFTD), semantic variant primary progressive aphasia (svPPA), PSP, corticobasal syndrome due to CBD, and non-fluent variant primary progressive aphasia (nfvPPA). Since network hyperexcitability is associated with faster cognitive decline in patients with AD [8–10] and possibly non-AD dementias, recognizing the risk and typical presentations of new-onset seizures across multiple forms of dementia is important. Correct diagnosis and early treatment of epilepsy in patients with dementia could improve quality of life, and trials will determine if such strategies could help stabilize or delay disease progression [26, 27].

MATERIALS AND METHODS

Patient Selection and Chart Review

Electronic medical records at the UCSF Memory and Aging Center were reviewed for patients evaluated between January 1, 2007 to December 31, 2013 (n=7,925) and who met diagnostic criteria for AD, FTD, or DLB (n=2,408) at their most recent clinical evaluation. Patients lacking sufficient records for review were excluded (n=183), as were those with diagnostic uncertainty who met probable criteria for multiple neurodegenerative diseases (n=333). Patients meeting both probable DLB and probable AD were not excluded due to the high coincidence of these forms of dementia, and were included in the DLB cohort [28, 29]. Patients meeting probable AD and probable corticobasal syndrome criteria were included in the AD cohort [30].

Patients with seizure risk factors were excluded, including those with remote history of seizures (defined as seizure onset at least 10 years prior to symptoms of neurodegenerative disease; n=16) or those with previous seizures provoked by cortical lesions, acute metabolic disorders, or subdural hematomas (n=25). This approach corresponds with exclusion criteria

in similar studies investigating seizures in dementia patients [31, 32] Records of patients with seizures were additionally reviewed to ascertain whether patients were taking bupropion or typical antipsychotics at the time of their first unprovoked seizure, given the ability of these medications to lower seizure threshold [33]. One of 78 patients with new-onset seizures included in this study was taking bupropion concurrent with their first seizure, although it was only taken once a week, and none were taking typical antipsychotics. Patients with a history of provoked myoclonus, such as drug-induced (n=5), were excluded. The remaining 1,846 patients were categorized into diagnostic cohorts based on their syndrome: AD (n=1,320), DLB (n=178; consisting of 149 DLB [28] and 29 DLB-AD [28, 29]) cases, and FTD (n=348; consisting of 115 bvFTD [34], 82 svPPA [35], 37 nfvPPA [35], 53 PSP [36], and 61 corticobasal syndrome due to CBD [30, 37]) cases. All subjects classified as AD in the present study met the “probable AD based on clinical criteria” guidelines outlined in McKhann et al. 2011 [29], including subjects diagnosed prior to 2011 who met the McKhann et al. 1984 criteria for probable AD [38]. Patient records were manually reviewed to determine age-at-onset of first neurodegenerative symptoms and date of dementia diagnosis. The neurologists’ evaluations included documentation of standardized forms querying for seizures and myoclonus.

Records were then compiled and searched using an automated text processing script that monitored the occurrence of word stems related to seizures (“seiz”, “epil”, “EEG”, “spell”, “shak”), myoclonus (“myoclon”, “jerk”), cognitive fluctuations (“fluc”), and head trauma (“head”). Records containing indications of possible epileptiform abnormalities were individually reviewed to determine if patients had experienced (a) one or more unprovoked seizures diagnosed by the clinician based on characteristic clinical features and/or epileptiform activity on EEG, (b) suspected but unconfirmed seizures, or (c) little to no clinical suspicion for seizures. Records with indications of myoclonus were reviewed to establish the date of myoclonus onset, defined as the date myoclonus was first stated in records if a specific date was not explicitly reported, and to screen for benign physiological myoclonus such as hypnagogic jerks. Seizures were classified according to established guidelines based on clinical presentation [39]. Inclusion within the seizure-positive group did not necessitate meeting diagnostic criteria for epilepsy, although a majority in this group (70 of 78) were subsequently diagnosed with epilepsy. Suspected but unconfirmed seizures referred to episodic symptoms that were suspicious for seizures to the clinician, but unconfirmed by witness accounts or epileptiform activity on concurrent or subsequent EEG, and did not meet criteria for inclusion as a seizure in the study. Clinical fluctuations in cognition, awareness, or attention, occurring within a single day, were based on either caregiver reports or observations by clinicians.

The electronic database was also searched for biomarker evidence of underlying AD pathology using positron emission tomography (PET) with amyloid-β binding radiotracers, including carbon 11–labeled Pittsburgh Compound B (PIB-PET) and 18F–AV-45 (florbetapir). PET scans were reviewed by a trained neurologist and classified as being either supportive or unsupportive of underlying AD pathology. Amyloid PET positivity in AD and FTD diagnosed participants was 93.5% (86/92) and 8.8% (8/91), respectively. Amyloid PET was performed on three patients with suspected DLB, of which 2 were positive and who were categorized as DLB-AD by clinical criteria. Baseline Mini-Mental State Examination

(MMSE) and Clinical Dementia Rating Sum-of-Boxes (CDR-B) scores obtained within 90 days of diagnosis of dementia and MMSE within 90 days of the first unprovoked seizure or myoclonus were extracted from the database when available. Records of patients with seizures were also reviewed for EEG results, including descriptions of epileptiform abnormalities and slowing indicative of cerebral dysfunction.

DNA extracted from whole blood samples was analyzed when available to assess for autosomal-dominant disease causing mutations.[8, 40] The genes included AD-causing mutations (amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*)) and FTD-causing mutations (chromosome 9 open reading frame 72 (*C9ORF72*), FUS RNA binding protein (*FUS*), granulin precursor (*GRN*), microtubule-associated protein tau (*MAPT*), and TAR DNA binding protein (*TDP43*)). Genetic variants associated with dementia risk and potential genetic disease modifiers were also assessed including apolipoprotein E (*APOE*) alleles,[8], *MAPT* Ala152Thr (A152T) substitution,[41] granulin precursor rs5848 allele,[42] *MAPT* H1/H2 haplotype,[8] transmembrane protein 106B (*TMEM106B*) rs1990622 allele,[43] and triggering receptor expressed on myeloid cells 2 (*TREM2*) rs75932628 allele.[44] Genotype data was available in 25–30% of all 1,846 subjects.

Epidemiological Analyses

Cumulative probability curves were calculated for the development of unprovoked seizures and myoclonus according to established Kaplan-Meier failure methods. Person-time contributing to Kaplan-Meier curves was calculated from date of onset of cognitive or motor symptoms until one of two criteria was met: (a) a new-onset seizure or new-onset myoclonus occurred, or (b) the date of the last available physician's note. Detailed notes from the time of death were unavailable; therefore, patients were censored at last available follow-up.

Incidence rates were calculated for new-onset seizures and myoclonus according to established formulas [45]. Patients contributed a maximum of eight years observed person-time (January 1st 2006 to December 31st 2013) and were censored as described above for cumulative incidence. Rates were then compared to corresponding incidence rates in general populations established by large-scale epidemiological studies of seizures [46] and myoclonus [47] to generate incidence rate ratios (IRR), the ratios of incidence rates in disease groups to incidence rates in age-matched control populations. The onset of seizures and myoclonus in all patient groups tended to cluster near the time of diagnosis. Therefore, patients without seizures or myoclonus were stratified according to age at dementia diagnosis.

Ethics

This study underwent review and was approved by the University of California, San Francisco Committee on Human Research.

Statistical analyses

All statistical analyses were conducted using Stata 14 software, and tests were computed at two-tailed alpha = 0.05, with Bonferroni corrections for multiple comparisons when

necessary. Non-parametric tests were applied to compare non-normally distributed demographic and clinical data. Prevalence data was compared using X^2 test, and post-hoc pairwise comparisons were subsequently carried out applying the generalized linear model. Cumulative incidence curves were compared by age-at-diagnosis-stratified log-rank test to account for the influence of age on the presentation of seizures and myoclonus. Genetic data were tested for associations of autosomal-dominant disease causing mutations with seizures and myoclonus in AD (genes *APP*, *PSEN1*, and *PSEN2*) and FTD (genes *C9ORF72*, *FUS*, *GRN*, *MAPT*, and *TDP43)* by Fisher's exact test. Genetic variants were also tested for associations with seizures and myoclonus across all subjects, as well as within each diagnostic cohort (AD, DLB, and FTD) by Fisher's exact test correcting for multiple comparisons. A logistic regression model was developed to estimate the independent effects of age-at-onset, diagnosis, and MMSE on the likelihood of developing seizures or myoclonus (see Supplementary Methods).

RESULTS

Demographics

Demographic information of participants is shown in Table 1. Patients with AD were predominately female whereas those with DLB were predominately male. FTD participants were younger at symptom onset and had more years of education compared to AD and DLB participants. Supplementary Table 1 presents demographics of the sample population by secondary diagnosis, including AD, DLB, DLB-AD, svPPA, bvFTD, PSP, CBD, and nfvPPA.

Incidence of Seizures and Myoclonus Differs by Dementia Type

The cumulative probability of developing seizures across diagnosis groups was 11.5%, and cumulative probability of developing myoclonus was 42.1%, as shown in Figure 1A. Figure 1B displays cumulative seizure probability curves of the three primary dementia cohorts. While the prevalence of new-onset seizures and myoclonus did not differ between the three groups (Table 2), their cumulative probabilities were distinct. The lengths of the observation periods in which seizures could occur for cumulative probability analysis did not significantly differ (Kruskal-Wallis $p = 0.20$; AD median 5.2 years, IQR 3.3 – 7.6; DLB median 5.5 years, IQR 3.7 – 8.3; FTD median 5.5 years, IQR 3.6 – 7.8). The seizure probability reached 13.4% in AD, 14.7% in DLB, and 3.0% in FTD, and the three curves were significantly different. For myoclonus, the cumulative probability was highest in DLB, reaching 58.1%, and the probability curves for the three cohorts were significantly different as well (Figure 1C). Incidence rates of seizures compared to age-matched controls were nearly 10 times higher in patients with AD and DLB, and 6 times higher in patients with FTD (Table 3). The incidence rate of myoclonus was 689 to 1,481 times higher in dementia patients than in age-matched controls.

Figure 2 displays age-stratified incidence rates of seizures and myoclonus for the three dementia cohorts, as well as the incidence rate ratios (IRR), the ratios of incidence rates in dementia groups to incidence rates in age-matched control populations. The seizure IRR increased with earlier age in AD (<50 IRR 126.7, 50–69 IRR 20.7, 70+ IRR 1.8, $p < 0.0001$)

(Figure 2A). The corresponding incidence rates of seizures in AD showed a similar age-related pattern (Figure 2C). The seizure IRR also increased with earlier age in FTD (<50 IRR 53.4, 50–69 IRR 9.4, 70+ IRR 0, p = 0.012), although the FTD cohort included only 11 patients in the youngest stratum. Additionally, no DLB patients were diagnosed before age 50. Myoclonus IRR increased with earlier age for patients in all three groups (Figure 2B). This relationship was also evident in the absolute incidence rates for AD and DLB but not FTD (Figure 2D).

Suspected but unconfirmed seizures, as well as apparent non-epileptic fluctuations in cognition and awareness, were most prevalent in patients with DLB (Table 2). Myoclonus was also most prevalent in DLB, followed by FTD. Supplementary Table 4 contains the prevalence of new-onset seizures and myoclonus at the level of dementia subtypes. Of the dementia subtypes, the group meeting probable criteria for both DLB and AD (DLB-AD) had the highest prevalence of seizures (20.7%), whereas none of the patients with svPPA had seizures. Myoclonus was most prevalent in the CBD group (41.0%) and least prevalent in the svPPA group (4.9%). Of 78 patients with seizures, one bvFTD patient had an autosomal-dominant *GRN* mutation and one AD patient had an autosomal-dominant *PSEN1* mutation. Of 205 patients with myoclonus, one had an autosomal-dominant form of AD (same *PSEN1* case with seizures). All remaining patients with evidence of hyperexcitability had sporadic forms of dementia. In analyses limited to patients with syndromes that can be caused by autosomal-dominant mutations, there were no statistically significant differences in the frequencies of mutations in patients with or without new-onset seizures or myoclonus (Fisher's exact test). There also were no significant associations between genetic variants that modify dementia risk or clinical presentation and development of new-onset seizures or myoclonus when assessed within each diagnostic group or pooled across all patients (Fisher's exact test, Supplementary Table 3).

Temporal Associations between Seizures and Myoclonus and Dementia

Seizures began an average of 3.9 ± 3.9 standard deviation years after the onset of cognitive or motor decline, whereas myoclonus began 5.4 ± 3.0 years after symptom onset (Figure 3). The time difference between onset of seizures or myoclonus and onset of dementia did not differ between dementia syndromes (Kruskal-Wallis). Seizures and myoclonus were significantly associated; 33.3% of patients with seizures had myoclonus, whereas 10.1% of patients without seizures had myoclonus ($p<0.001$, X^2). Of the 26 patients with both seizures and myoclonus, seizures preceded myoclonus in 13 and they occurred simultaneously in 2. The median difference between onset of seizure and myoclonus in patients with both symptoms was 1.2 years (IQR 0.6 – 3.6).

In logistic regression analyses that included diagnosis, age-at-onset, and disease severity measured by MMSE as independent predictors of seizures and myoclonus, MMSE was not associated with myoclonus (p = 0.40) or seizures (p = 0.65) (Supplementary Tables 5 and 6). As suggested by the absolute rates of seizures and myoclonus within each age stratum (Figure 2C and D), seizures were associated with younger age in AD ($p < 0.001$) and older age in DLB (p = 0.04), and myoclonus was associated with younger age in AD ($p < 0.001$). See Supplementary Results for a complete description of these models.

Seizure Semiology

Of 78 patients identified with new-onset seizures, sufficient information to classify seizures was available for 71. Seizures were exclusively non-motor in 54.9% of cases (39 of 71), and were classified as generalized, without clear focal or lateralizing symptoms, in 52.1% (37 of 71). There were no significant relationships between dementia syndrome and the frequency of motor versus non-motor or generalized versus focal onset seizures (Fisher exact test). Clinical characteristics of these seizures are summarized by dementia syndrome in Table 4, and electroencephalography (EEG) results for patients with seizures are summarized in Table 5.

DISCUSSION

The results of this study indicate that development of seizures and myoclonus differs amongst patients with the three most common forms of neurodegenerative disease: AD, DLB, and FTD. Overall, allowing for co-pathology, the results suggest that seizure propensity is highest when Aβ or α-synuclein pathology is present (e.g., AD, DLB, and DLB-AD), whereas myoclonus propensity, at least in early stages of disease, is higher in primary tau disorders (e.g., CBD) or when α-synuclein is present. Notably, pathological tau is common to the above disorders. In this regard, it is informative that patients with svPPA, which is commonly a TDP-43 disorder that lacks tau co-pathology [48], had the lowest rates of seizures and myoclonus. These findings support complex mechanisms of network hyperexcitability in the different dementia syndromes, reflecting their heterogeneous neuropathology.

Cumulative Incidence, Prevalence, and Clinical Presentations

Patients with AD and DLB had a higher cumulative incidence of seizures than FTD, although they did not differ significantly in terms of point prevalence of seizures. The overall cumulative probability of developing seizures for patients in this study is in close agreement with other studies of seizures in neurodegenerative diseases [2, 32, 49].

Seizures were more frequently suspected and unconfirmed in DLB compared to both AD and FTD. This finding may be attributable to the fluctuations in cognition and awareness that are hallmarks of DLB diagnosis and were present in a majority of patients with the disease. Previous literature has indicated that seizures can precede or follow cognitive symptoms in both AD and non-AD dementias [4, 5, 31, 50, 51]. The characteristics of seizure presentation in this study agree with those findings and provide more detail about seizure onset within the DLB and FTD cohorts. The seizures in patients with AD, DLB, and FTD lacked obvious distinguishing clinical features, suggesting that seizure semiology is not specific to the neurodegenerative syndrome.

In terms of myoclonus, DLB patients had a consistently higher cumulative incidence of myoclonus than patients with AD or FTD. Myoclonus probability in AD increased gradually over time, whereas in FTD the probability rose steeply in the years immediately following disease onset. These different patterns could partially reflect inclusion of myoclonus in some FTD diagnostic criteria such as CBD, since the upslope was near the time interval when

diagnosis was most likely. Patients with DLB also had a high point prevalence of myoclonus, significantly higher than the prevalence in both AD and FTD and similar to values obtained in pathologically confirmed cases [52].

Temporal Relationship between Symptoms of Hyperexcitability and Onset of Disease

Seizure rates in were markedly increased in younger patients with AD and, to a lesser extent, FTD. The strong relationship between younger age and seizure incidence in AD is strikingly similar to previous reports [2], and our findings extend on previous data to show an even higher seizure risk when disease starts before age 50. In addition to the age-stratified analysis that compared incidence rates with control populations, a predictive model that included age-at-onset as a continuous variable demonstrated a similar relationship between younger age and occurrence of seizures in AD. This model also revealed an association between older age and seizures in DLB, as suggested by Figure 2C, which could reflect development of AD pathology or other comorbidities in the DLB group with aging.

Myoclonus rates were increased at younger ages in all three dementia syndromes, in comparison with age-matched control populations. The relationship between young age and occurrence of myoclonus was strongest in AD, as indicated by the supplementary logistic regression model. Taken together, these findings indicate that clinical signs of hyperexcitability develop more commonly with younger age in AD and variably in relation to age in FTD and DLB.

Both seizures and myoclonus developed early in disease course in all three dementias, and in many cases the two features coexisted. Associations between seizures and myoclonus have also been reported in patients with early-onset AD, and are suggested to have a common underlying cortical pathology [16]. From a clinical perspective, recognizing the co-occurrence of seizures and myoclonus may guide clinicians to their earlier detection and treatment. The development of seizures and/or myoclonus might hasten disease onset or represent a more aggressive neurodegenerative phenotype. The cohort contained only two patients with seizures or myoclonus in the context of an early-onset, familial form of disease, raising the possibility that there are other genetic or epigenetic predispositions to seizures and myoclonus in early-onset dementia cases.

Pathological Implications

The observation that the DLB-AD group had the highest prevalence of seizures (20.7%) amongst the dementia subtypes (Supplementary Table 2) warrants further discussion. Increased seizure risk in such cases could be simply attributed to increased neuropathological burden associated with dual disease, but there may also be an epileptogenic synergy between the two disease processes. Such synergistic interactions have been previously demonstrated in doubly transgenic mice expressing human α-synuclein and APP [53]. In contrast, no seizures were observed in the svPPA cohort, and this group had the lowest incidence of myoclonus among the FTD subtypes. This result is surprising given the high correlation of svPPA with ubiquitin- and TDP-43-positive pathology in the temporal lobes, and may reflect relatively confined involvement of anterior temporal lobe structures or lesser influence of TDP-43 on synaptic activity [35, 54]. Possibly related to the lower

incidence of network hyperexcitability in svPPA, this group also has a longer survival rate than other variants of FTD [55].

Strengths and Limitations

A major strength of this study is its novel exploration of differences in susceptibility to network hyperexcitability in specific types of dementia. Some limitations should also be discussed. The retrospective nature of the analysis limited our ability to precisely distinguish the differences in seizure and myoclonus rates, and we were not able to employ validated tools common to prospective cohort studies. EEG confirmation of seizures was not obtained in all cases; however, it should be noted that routine EEG has low sensitivity in capturing epileptiform activity, even in patients with established seizure disorders [56]. Since clinical seizures were not highly prevalent, the DLB and FTD groups provide a relatively small sample size for epidemiological analysis of seizure development. Additionally, selection bias towards patients with rare forms of dementia who are suitable for research may reduce the generalizability of the findings. Demographic data in this study, however, do suggest that patients are somewhat representative of broader populations. For example, sex distributions are in line with previous reports in patients with neurodegenerative diseases [57, 58], and rates of amyloid PET positivity in patients with AD and FTD are consistent with results from broader dementia populations [59]. Finally, lack of autopsy information constrains our ability to accurately gauge the precision of clinical diagnosis and degree of co-pathology. The current results provide groundwork for future studies to prospectively elucidate precise mechanisms by which different disease processes might contribute to neural network hyperexcitability.

CONCLUSION

Seizures and myoclonus occur in AD, DLB, and FTD at higher rates than in the general population, and should therefore raise suspicion of a dementia diagnosis when other etiologies have been ruled out. This study's findings illustrate that network hyperexcitability may develop from pathomechanisms that vary between neurodegenerative diseases and that clinical signs of hyperexcitability often appear near the time of dementia diagnosis.

Antiseizure drug therapy improves cognitive and behavioral function in transgenic mouse models of AD, and clinical trials using antiseizure drugs for AD-associated network hyperexcitability are ongoing. The findings of this study raise the possibility that similar strategies might benefit patients with FTD and DLB. Earlier detection of network hyperexcitability in patients with dementia, and more precise understanding of the mechanisms involved, could lead to better treatment of the disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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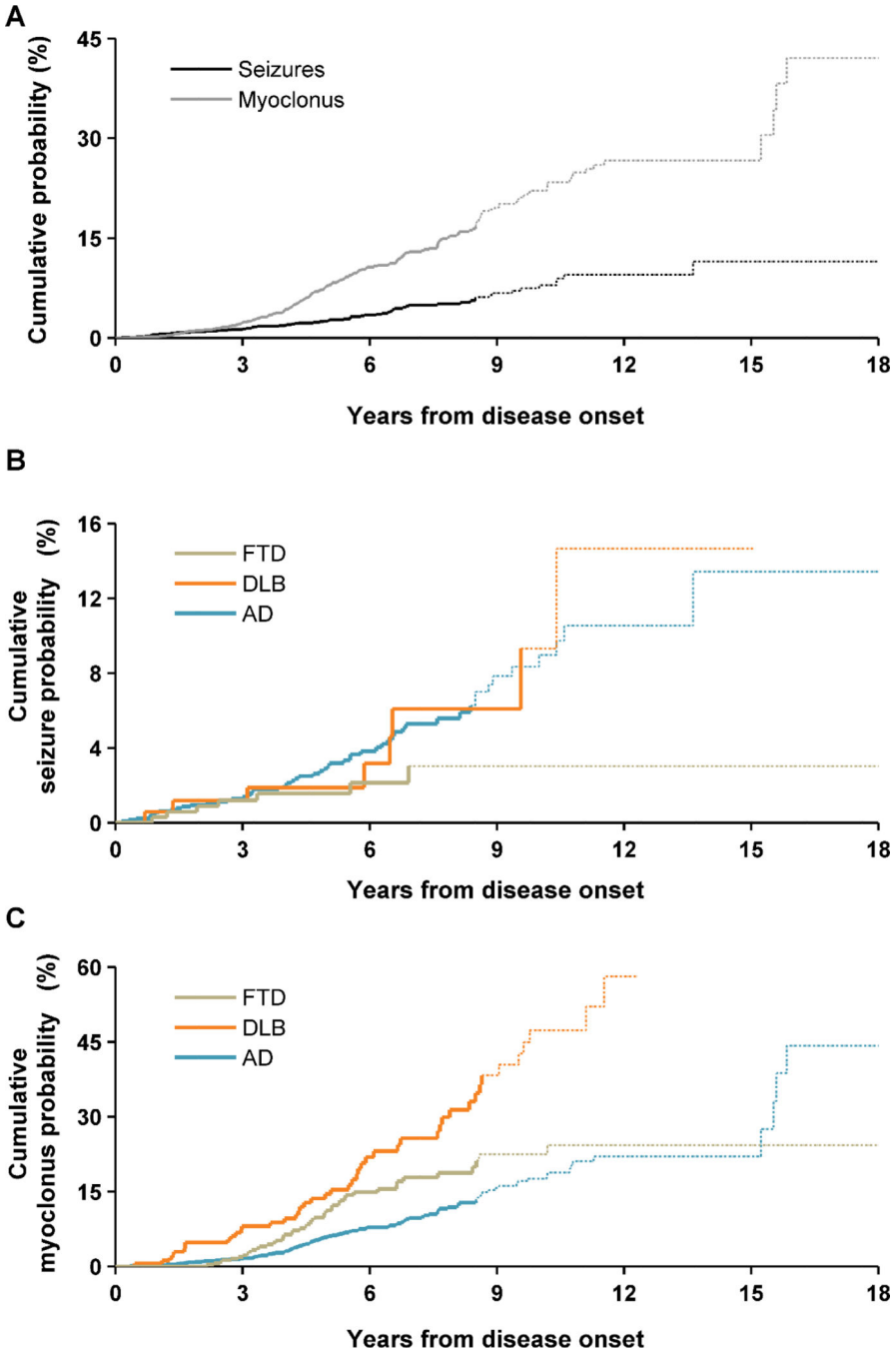

Figure 1.

Cumulative probability curves of new-onset seizures and myoclonus. (A) Cumulative probability curves for all patients. (B and C) Cumulative probability curves of new-onset seizures (B) and myoclonus (C), by diagnostic cohort (panel B, p=0.005 and panel C, p<0.0001, age-at-diagnosis-stratified log-rank test comparing the three groups). Curves become dotted at the point where 80% of patients are censored.

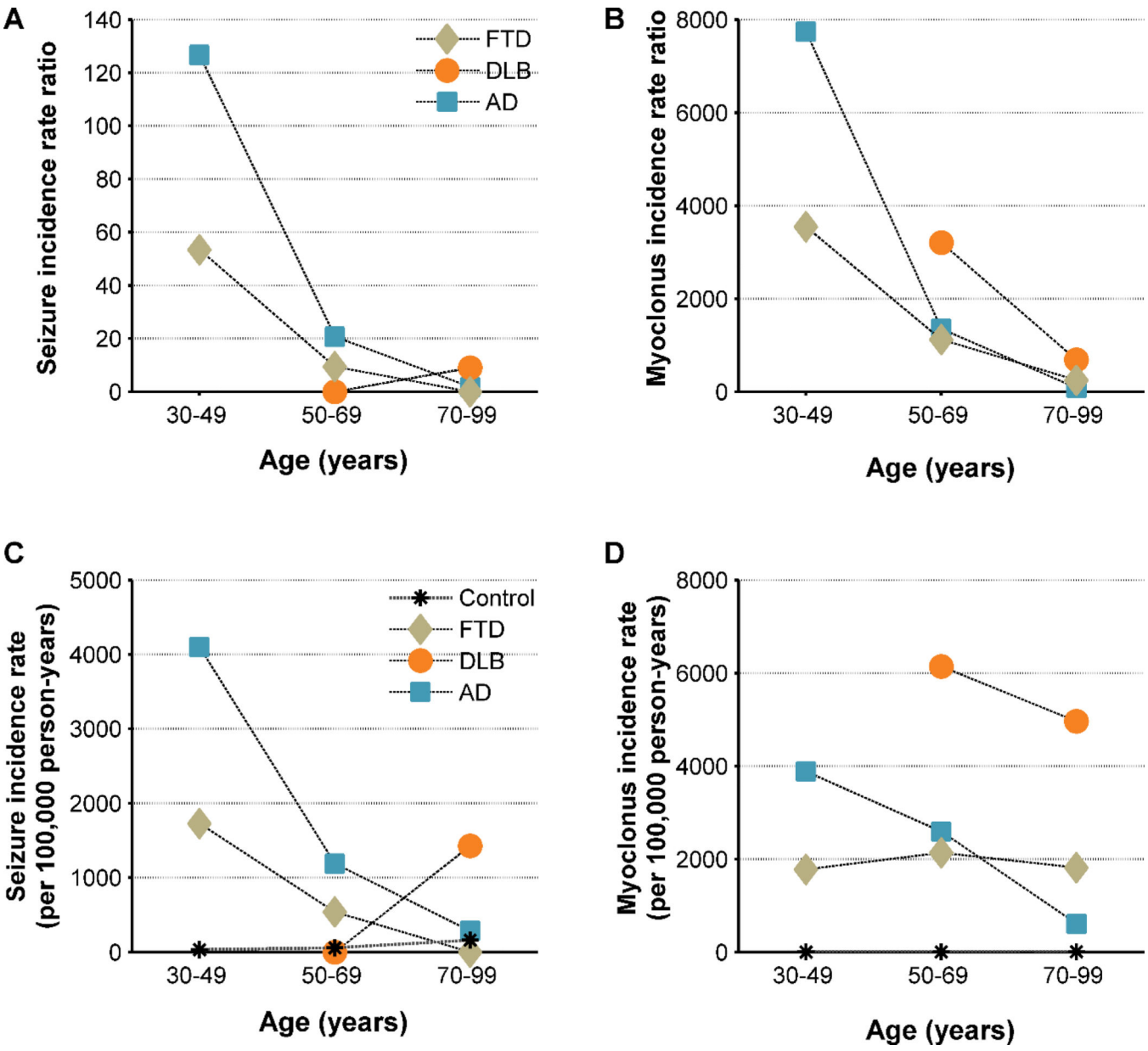

Figure 2.

Age-stratified incidence rate ratios (IRR), the ratios of incidence rates in dementia groups to incidence rates in age-matched control populations, and raw incidence rates for new-onset seizures and myoclonus, by diagnostic cohort. (A and B) IRR for new-onset seizures (A) and myoclonus (B) (panel A, seizure IRR increased with earlier age in AD, $p<0.0001$, and FTD, $p=0.012$, X^2 test, and panel B, myoclonus IRR increased with earlier age in AD, $p<0.0001$, DLB, $p=0.022$, and FTD, $p=0.033$, X^2 test). The IRR values and 95% confidence intervals are provided in Supplementary Table 2. (C and D) Component incidence rates from patients and control data in epidemiological studies[46, 47] for seizures (C) and myoclonus (D). No patients with DLB were seen in the stratum of 30 – 49 years of age.

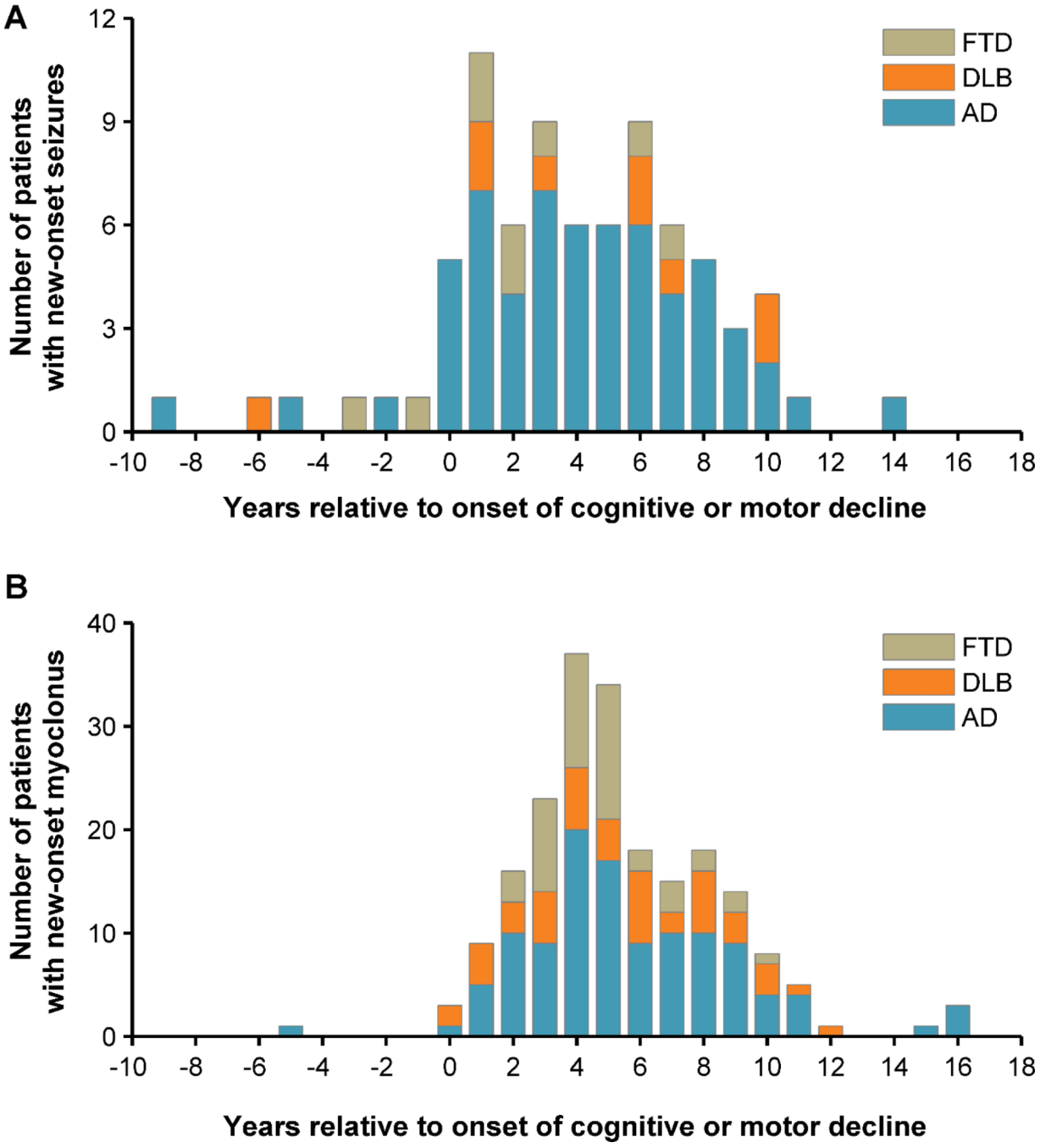

Figure 3.

Onset of seizures and myoclonus in relation to onset of cognitive or motor decline, by diagnostic cohort. (A) Occurrence of new-onset seizures in relation to age-at-onset of cognitive or motor decline. (B) Occurrence of myoclonus in relation to age-at-onset of cognitive or motor decline.

Table 1

Patient demographics and clinical information

	AD (n = 1,320)	DLB (n = 178)	FTD (n = 348)	p value
Female (%)	60.5	39.3	51.2	< 0.001[b]
Right-handed (%)	90.9	88.8	91.6	0.557[c]
Education (median (IQR))	16 (12 – 18)	16 (13 – 18)	16 (14 – 18)	0.030[d]
Age-at-onset (median (IQR))[a]	71 (62 – 78)	71 (64 – 76)	61 (56 – 67)	0.0001[e]
Years from onset to diagnosis (median (IQR))	4 (2 – 6)	4 (2 – 6)	4 (3 – 6)	0.378[f]
Age-at-diagnosis (median (IQR))	75 (67 – 82)	74 (68 – 79)	65 (60– 71)	0.0001[g]
MMSE nearest diagnosis (median (IQR))	22 (18 – 25)	25 (22 – 27)	26 (23 – 28)	0.0001[h]
CDR-B nearest diagnosis (median (IQR))	4.5 (3.5 – 6)	4.5 (3 – 9)	4 (2 – 7.3)	0.592[f]

[a] Age-at-onset refers to onset of cognitive or motor symptoms.

[b] X^2 test. All comparisons significantly differ with X^2 corrected for multiple corrections. AD vs. DLB, p <0.001; DLB vs. FTD, p=0.010; and AD vs. FTD, p=0.002 (Mann-Whitney).

[c] X^2 test.

[d] Kruskal-Wallis. FTD had more years of education than AD, p=0.011 (Mann-Whitney).

[e] Kruskal-Wallis. Age-at-onset significantly lower in FTD vs. AD, p<0.0001 and DLB, p<0.0001 (Mann-Whitney).

[f] Kruskal-Wallis.

[g] Kruskal-Wallis. Age-at-diagnosis significantly lower in FTD vs. AD, p<0.0001 and DLB, p<0.0001 (Mann-Whitney).

[h] Kruskal-Wallis. MMSE significantly lower in AD vs. DLB, p < 0.0001 and FTD, p < 0.0001. MMSE significantly lower in DLB vs. FTD, p = 0.028 (Mann-Whitney).

AD, Alzheimer's disease; CDR-B, Clinical Dementia Rating Box Score; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; IQR, interquartile range; MMSE, Mini-Mental Status Examination.

Table 2

Prevalence of new-onset seizures and other potential indicators of network hyperexcitability

	New-onset seizures (%)	Suspected but unconfirmed seizures (%)	Myoclonus (%)	Clinical fluctuations (%)
AD (n = 1,320)	4.5	3.8	8.5	10.2
DLB (n = 178)	5.1	14.6	27.0	69.1
FTD (n = 348)	2.6	2.3	12.9	6.9
p value[a]	0.229	< 0.001[b]	< 0.001[b,c]	< 0.001[b†]

[a] X^2 test.

[b] DLB significantly higher than FTD, p<0.001 and AD, p<0.001.

[c] FTD significantly higher than AD, p=0.017.

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia.

Table 3

Incidence rates of new-onset seizures and myoclonus in dementia groups, expressed as ratios relative to age-matched control populations [46, 47].

	New-onset seizures	Myoclonus
AD	9.7 (6.8 – 13.7)	689.2 (383.9 – 1,343)
DLB	10.0 (4.2 – 20.4)	1,481 (752.5 – 3,179)
FTD	6.4 (2.7 – 13.0)	1,097 (573.1 – 2,239)

Values in parentheses are 95% confidence intervals.

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia.

Table 4

Clinical characteristic of seizures in patients with neurodegenerative diseases

	AD (n = 56)	DLB (n = 8)	FTD (n = 7)	p value[a]
Generalized/Focal	29/27	6/2	2/5	0.246
Non-motor/Motor	32/24	4/4	3/4	0.763

[a]Fisher exact test.

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia.

Table 5

Electroencephalographic characteristics of 78 patients with seizures

Cohort Characteristic	Value (n / total n (%))
Patients with EEG	48/78 (61.5)
At least one >12 hour EEG acquired	12/48 (25.0)
EEG Result[a]	
Normal	11/48 (22.9)
Slowing	31/48 (64.6)
Diffuse	19/31 (61.3)
Focal	15/31 (48.4)
Epileptiform	22/48 (45.8)
Asymmetric	16/22 (72.7)
Focal temporal or frontotemporal	13/22 (59.1)
Generalized	3/22 (13.6)

[a]Results pooled across all available EEG acquisitions for each patient. Patients may contribute to more than one result