Original Article
Journal of Epilepsy Research
pISSN 2233-6249 / eISSN 2233-6257

Prevalance of Non-Provoke Generalize Tonic-Clonic Seizure in Sporadic Alzheimer's Disease

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Background and Purpose: Alzheimer's disease (AD) and epileptic seizure are among the most common health problems in the elderly population. This study aimed to estimate the prevalence rate and predictors of seizures in sporadic AD patients.

Methods: The study was conducted by retrospectively for a period of 10 years examining the file records. Patients were selected among the patients diagnosed with probable sporadic late onset AD according to the National Institute of Neurological Communicative Disorders and Stroke AD and related disorders association criteria and the diagnostic and statistical manual of mental disorders (n=451). In our 213 sporadic AD patients who were followed up regularly and had a follow up examination in the last 6 months, the file records were examined, scanned and questioned for the presence of epileptic seizures.

Results: The prevalence of non provoked generalized tonic clonic seizures in sporadic AD was found to be 6.57% (n=14). Neuroleptic use, presence of diabetes mellitus (DM) and/or treatment, presence of ischemic heart disease (IHD) and/or treatment were found to be 2.99 times, 1.91 times and 3.09 times higher in our patients who had seizures, respectively. When the factors that can affect seizures were examined, the use of neuroleptics and the presence of IHD and/or treatment were found to be statistically significant in terms of the risk of seizure in AD.

Conclusions: The use of neuroleptics, the presence of IHD and DM and/or their medications could facilitate the development of unprovoked generalized tonic clonic seizures in sporadic AD. It is doubtful whether the seizures are primary or secondary generalized. **(2024;14:66-72)**

Key words: Dementia, Alzheimer's disease, Seizure

Received May 26, 2024
Revised July 1, 2024
Accepted July 18, 2024

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Introduction

As the number of older adults continues to increase, the health problems of the elderly population are also increasing. Alzhemier's disease (AD) and epileptic seizure are among the most common health problems in the elderly population.[1-3] These two separate clinical pictures in the elderly population are sometimes seen together in the same person, which has made some wonder about the relationship between the two. Some studies have reported that the prevalence of epileptic seizures is higher in patients with AD when compared to age-matched cognitively normal populations. Other studies suggest that the presence of epileptic seizures and epilepsy in AD may be similar to or slightly different from the general population. Moreover, some studies report a bidirectional relationship between epilepsy and dementia.[4-7]

The questions of whether the presence of epileptic seizures paves the way for the development of AD or whether the neuropathological changes in the AD brain trigger the development of epileptic seizures are still not clearly answered. However, there have been studies advocating both different views.[8,9] The important problem is that there are still unclear points in the association of dementia and epilepsy, especially regarding the frequency and causes. The aim of this study was to assess prevalence rates of seizures in patients with sporadic AD and to identify potential risk factors of epileptic seizures. Also, comorbid conditions were assessed in AD patients, and it was investigated whether they could pose a potential risk in the development

of epileptic seizures.

Methods

Retrospective study approval was given by the ethics committee on April 16, 2021 with the number 2021/E-62977267-000-6344. The study was conducted by retrospectively for a period of 10 years (between January 1, 2011 and November 30, 2021), examining the file records of our patients who were admitted to our dementia outpatient clinic. The patients with amnesia have been examined about their systematical, neurological systems, neuroradiological examinations and detailed biochemical investigations, which is evaluated according to our routine standard procedure that rules out the reversible causes of dementia. Patients with secondary dementia due to reversible or correctable causes were not included in the file scanning in this study. Eight hundred seventy-three patient files were scanned retrospectively (n=873).

Those with advanced liver-kidney-heart failure, orthostatic hypotension, those with pacemakers and heart rhythm disorders, those with suspicion of malignancy-autoimmunity and encephalopathy were excluded from the study (n=50).

Additionally, a total of 372 more patients were excluded from the study, including patients with neuroradiologically detected vascular-structural lesions other than atrophy, patients with dementia whose type of dementia could not be determined (n=120), vascular dementia patients (n=144) and frontotemporal dementia patients (n=108).

Study subjects were selected among the patients diagnosed with probable sporadic late onset AD according to the National Institute of Neurological Communicative Disorders and Stroke-AD and related disorders association criteria and the diagnostic and statistical manual of mental disorders (n=451). Among these 451 patients, those who did not come for regular follow-up, those who had incomplete information, and those who could not be examined in the last 6 months were also excluded from the study (n=238 patients). In our 213 sporadic AD patients who were followed up regularly and had a follow-up examination in the last 6 months, the file records were examined, scanned and questioned for the presence of epileptic seizures (Fig. 1). Moreover, seizure information was taken retrospectively from the records of the observer caregivers and emergency health teams and from our dementia outpatient clinic records. Seizure history was questioned with the seizure inquiry form (Supplementary Material 1).

Our patients were also screened and examined in terms of co-morbid diseases other than Alzheimer's dementia and the medications they used. Use of antidementia, use of antidepressants, use of neuroleptics, presence and/or treatment of hypertension, presence and/or treatment of hyperlipidemia, presence and/or treatment of diabetes mellitus (DM), low high-density lipoprotein cholesterol (HDL-C) (HDL-C below 40 mg/dL in women and 50 mg/dL in men), fasting blood sugar elevation (fasting blood sugar value is over 100 mg/dL), and presence and/or treatment of ischemic heart disease (IHD) were recorded. The contribution of these data found in the file records was investigated for the development of seizures in AD. Electroencephalography examinations (EEG) are our clinical routine for every patient with a definitive seizure or suspicion of seizure and EEG were performed during the interictal period.

We performed computerized brain tomography or cranial magnetic resonance imaging for all patients. No quantitative measure-

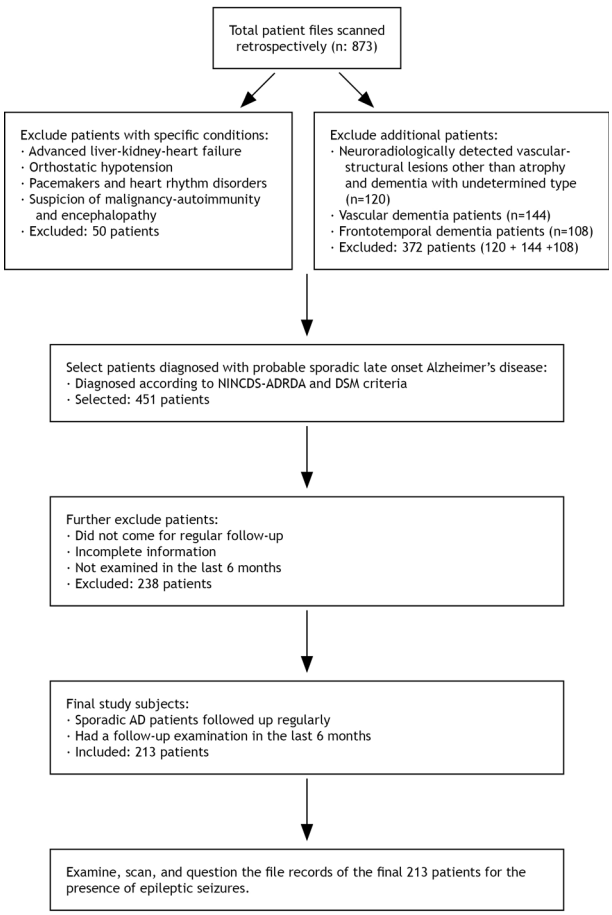

Figure 1. Patient selection process for study. NINCDS-ADRDA, National Institute of Neurological and Commnicative Disorders and Stroke and the Alzheimer's disease and related disorders association; DSM, diagnostic and statistical manual of mental disorders; AD, Alzheimer's disease.

ments were made to grade atrophy. We conducted a mini mental test (MMT), a clock drawing test, clinical dementia rating (CDR), and geriatric depression scale for each patient. We also surveyed the daily living activities of the patients. These routine follow-up examinations, accompanied by a neurological examination, are conducted when our patients are first diagnosed, during their follow-up, and in case an unexpected situation occurs outside the normal course. For patients with seizures, examinations are performed during the month when seizures occur and for patients without seizures, examinations are conducted during the last 6-month follow-up visits.

Statistical analysis

In this study, statistical analyzes were made with the NCSS 2007 package program (NCSS, Kaysville, UT, USA). In the evaluation of the data, besides descriptive statistical methods (mean±standard deviation), independent *t*-test in comparison of paired groups, chi-square test and odd's ratio in comparison of qualitative data were used. Logistic regression analysis was used to determine the factors that can affect the seizure. The results were evaluated at the significance level of $p<0.05$, at a 95% confidence interval.

Results

Our sporadic AD patients that we could document were 213 patients, 99 males and 114 females. The mean age was 73.24±7.81 and the mean MMT was 16.97±4.79. All patients were receiving anti-dementia treatment (cholinesterase inhibitor, cholinesterase inhibitor and memantine or memantine). None of the patients had a history of epileptic seizures or epilepsy before the complaint of forgetfulness has begun.

Focal epileptic seizures were not recorded in any of our patients. No information suggesting a focal seizure could be obtained from the questions in Supplementary Material 1 and file records, and information that could be related to a focal seizure was not secure. Clear focal or non-motor seizure information was not found in our file records. No patient was taken to the emergency room with a focal seizure. Reliable-clear-accurate information was only about generalized tonic-clonic epileptic seizures and it was seen in 17 patients.

Systemic-neurological and neuro-imaging examination information was obtained by reviewing the emergency outpatient clinic records of patients who were examined and evaluated when they had a seizure. Three of these 17 patients were evaluated as provoked seizures (two metabolic electrolyte disturbances and one infection and sepsis). The remaining 14 patients had seizures defined as non-provoked generalized tonic-clonic seizures. None of the patients with seizures had new developed structural lesions. Thus, the prevalence of non-provoked generalized tonic-clonic seizures in AD was found to be 6.57% (n=14).

Table 1. Comparison of age, MMT scores, duration of complaints before diagnosis of AD in patients with and without unprovoked epileptic seizures

	E.Seizure (-) (n=196)	E.Seizure (+) (n=14)	*t*	*p*-value
Age (years)*	73.35±7.96	71.57±6.07	0.555	0.580
MMT†	16.92±4.8	17.64±4.65	0.543	0.588
Duration (years)‡	3.93±2.74	3.79±2.96	0.194	0.846

MMT, mini mental test; AD, Alzheimer's disease; E.Seizure, epileptic seizure.
*The age at which patients had epileptic seizures and those who did not have seizures when they were last examined.
†MMT scores at the last examination of patients who did not experience seizures with MMT in the first month after epileptic seizure.
‡Duration of symptoms related to amnesia before AD diagnosis.

Table 2. Distribution of CDR stages of the AD patients with non-provoked epileptic seizures and the patients without seizures (χ^2: 0.02; p=0.903)

CDR	E.Seizure (-) (n=196)	E.Seizure (+) (n=14)	Total AD
Stage 1	82 (41.8)	6 (42.9)	88 (41.9)
Stage 2	64 (32.7)	5 (35.7)	69 (32.9)
Stage 3	50 (25.5)	3 (21.4)	53 (25.2)
Total	196 (100.0)	14 (100.0)	210 (100.0)

Values are presented as number (%).
CDR, clinical dementia rating; AD, Alzheimer's disease; E.Seizure, epileptic seizure.

There was no statistical difference between AD patients with and without epileptic seizures according to age at which they had epileptic seizures, MMT values, and the duration of complaint of forgetfulness before the diagnosis of AD, at the date of their last examination (Table 1). Moreover, there was no statistically difference according to the clinical stages of the patients with and without seizures at the time of the last examination (Table 2).

The results were similar in terms of cholinesterase inhibitors and memantine treatment in our AD patients with and without seizures. Also, our AD patients with and without epileptic seizures were compared in terms of co-morbid diseases other than dementia and medications. Neuroleptic use, presence of DM and/or treatment, presence of IHD and/or treatment were found to be 2.99 times, 1.91 times, and 3.09 times higher in our patients who had seizures, respectively (Table 3). When the factors that can affect seizures were examined, the use of neuroleptics and the presence of IHD and/or treatment were found to be statistically significant in terms of the risk of seizure in AD (Table 4).

Ictal EEG recording could not be made in any of our patients. Interictal EEG was examined in all patients with seizures. Interictal EEG was evaluated as normal in 10 patients. Abnormal interictal EEG was seen in only four patients. These EEGs were in the form of nonspecific slow wave paroxysms based on diffuse organizational disorder (one patient) and diffuse disorganization disorder (three patients).

Discussion

The risk of developing seizures in Alzheimer's patients is higher than in healthy elderly people of similar age. It has been reported that in AD patients, the rate experiencing at least one unprovoked seizure varies widely, such as 5% to 64%.[10,11] This range is depending on the methodology, especially whether it is conducted retrospectively[12-16] or prospectively,[10,17-19] and the type of seizure investigated. The highest rates were given in studies involving hospitalization and autopsy.[11]

In our study, the prevalence of non-provoked generalized tonic-clonic seizures was found to be 6.57% (n=14). Our results were within the range of results obtained in retrospective[12-16] studies. None of our patients had a diagnosis of epileptic seizure or epilepsy before the diagnosis of AD. This rate was given as 6.80% in the retrospective study of Lozsadi and Larner.[14] In some studies, patients with knowledge of epileptic seizures in the years before AD diagnosis were excluded from the study.[4] In the institutions where we work,

Table 3. Co-morbidity and non-dementia medication status of AD patients with and without non-provoked epileptic seizures

	E.Seizure (-) (n=196)	E.Seizure (+) (n=14)	OR (95% CI)	χ^2
Male-female	90 (45.9)-106 (54.1)	9 (64.3)-5 (35.7)	1.11 (0.28-1.95)	1.76 (p=0.184)
Use of antidepressants+	92 (46.9)	4 (28.6)	0.45 (0.14-1.49)	1.81 (p=0.182)
Use of neuroleptics+	107 (54.6)	11 (78.6)	2.99 (0.81-11.06)	3.5 (p=0.081)
Presence and/or treatment of HT+	98 (50.0)	7 (50.0)		0 (p=1)
Presence and/or treatment of HpL+	100 (51.0)	5 (35.7)	0.53 (0.17-1.64)	1.22 (p=0.268)
Presence and/or treatment of DM+	34 (17.3)	4 (28.6)	1.91 (0.56-6.43)	1.1 (p=0.292)
Low HDL-C+	72 (36.7)	5 (35.7)	0.95 (0.31-2.96)	0.006 (p=0.939)
FBS elevation+	57 (29.1)	4 (28.6)	0.97 (0.29-3.23)	0.02 (p=0.968)
Presence and/or treatment of IHD+	59 (30.1)	8 (57.1)	3.09 (1.02-9.3)	4.39 (p=0.036)

Values are presented as number (%) unless otherwise indicated.
AD, Alzheimer's disease; E.Seizure, epileptic seizure; OR, odds ratio; CI, confidence interval; HT, hypertension; HpL, hyperlipidemia; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood sugar; IHD, ischemic heart disease.

Table 4. Factors that can affect the development of seizure in AD patients

	β	SE	p-value	Exp (β)	95% CI ExP (β)	
					Lower	Upper
Use of neuroleptics	-1.48	0.71	0.036	0.23	0.06	0.91
Presence and/or treatment of DM	-0.431	0.66	0.519	0.65	0.18	2.40
Presence and/or treatment of IHD	-1.38	0.67	0.039	0.25	0.07	0.93
Constant	-1.18	0.73	0.75	0.67		

AD, Alzheimer's disease; SE, standard error; Exp, exponential; CI, confidence interval; DM, diabetes mellitus; IHD, ischemic heart disease.

epileptic patients are followed up in the different epilepsy outpatient clinics, and we think that these different follow-up outpatient clinics have affected the epilepsy rates in the medical history information of our AD patients.

Studies have reported that patients with AD have had both generalized and complex partial seizures. Additionally, some studies have reported that nonmotor atonic and nonconvulsive seizures may also occur. Moreover, there are studies reporting that complex partial seizures are more common in AD.[15,16] Rao et al.[15] examined epileptic seizures and treatment results in neurodegenerative diseases and stated that complex partial seizures were higher in the patient groups with mild cognitive impairment, Alzheimer's, vascular dementia and Lewy body disease.

There was no clear information about focal onset seizure in our file records (emergency department records) and our retrospective seizure inquiry form. Despite this, we have received information that could suggest focal onset and secondary generalization in one of these 14 patients. However, there was no video recording, and the information was based solely on the caregiver's observation, who mentioned, "it's like twitching in the corner of the eye". The observation was also deemed suspicious. In our study, we could not obtain clear and accurate information about focal onset or non-motor seizures. It was clear that all of our patients who had seizures had generalized tonic-clonic seizures. Moreover, we also could not obtain clear and accurate information about non-motor generalized seizure or focal seizures. However, definitions of tonic clonic seizures were clear, descriptive, and reliable and witnessed.

Some studies have found that seizures recorded after the onset of dementia are more likely to occur in later stages of the disease.[11,20] However, others found that neither disease duration nor age of onset were significant risks for seizures in AD patients.[12,17] Another study reported that the presence of seizures in AD is not a common phenomenon but emphasized that younger age would be a predictor for the development of seizures in AD.[10] Furthermore, some studies have indicated that younger age was significantly associated with seizures in AD patients.[10,12,13,18]

Unlike these studies, we did not find a relationship between the ages, MMT and clinical stages of our AD patients with seizures and those without seizures. Our study consisted of screening patients with late-onset sporadic AD. Also, the ages and clinical stages of our AD patients with and without seizures were similar. We thought that these factors might have an impact on the fact that we did not find any age-related or CDR-related differences. In the longitudinal study of Baker et al.,[21] while there was no significant difference between patients with seizures and patients without seizures at the beginning, a faster clinical worsening was shown in patients with seizures over time. In our study, we compared the clinical status of our patients with seizures in the month of seizure to the clinical stages of our patients without seizures when we last examined them, but did not find any difference. Moreover, our study was retrospective and did not examine the clinical and mental progression of patients after they had a seizure. In addition to all these, the small number of patients in our study may also be effective in these results.

Studies investigating seizures in Alzheimer's mostly focus on data regarding prevalence or seizure type. In studies investigating the presence of epileptic seizures in AD, the number of studies examining in detail the effects of comorbidities, neuroleptic use, anti-dementia drugs, and antidepressant use on seizure development is limited. Although the proconvulsant effects of antidepressant drugs have been reported, it has been stated that this side effect is negligible at therapeutic doses.[22,23] Consistent with this information, the antidepressants we used in our study were citalopram and escitalopram, and they had no effect on the development of seizures.

A retrospective study from Asia investigated the incidence and risk factors of epileptic seizures in AD. Hypertension, hyperlipidemia, DM, heart failure, atrial fibrillation, autoimmune diseases, and etc. were not found to be a significant factor. Only age was cited as an independent determinant of seizures in AD.[24] Our study was retrospective, like the study of Cheng et al.[24] However, unlike their study, we found that DM, IHD and neuroleptic use was significantly higher in AD patients with seizures, and neuroleptic use was the most important risk factor for generalized tonic-clonic seizure. Unfortunately, we could not clearly find DM and IHD medications and their doses in our file documents. On the other hand, the neuroleptics used were haloperidol drops and quetiapine. It is known that the use of antipsychotics increases the risk of seizures.[25] Quetiapine and haloperidol we use in our patients also have this effect. This result is also compatible with the results of Irizarry et al.,[26] which stated that quetiapine use increases the risk of seizures in AD patients. Also, they have reported that memantine, used in the treatment of dementia, poses a risk for seizures.[26]

On the other hand, although another study reported a relationship between acetylcholinesterase inhibitors and seizures,[27] there are also studies that do not support this view.[28,29] We found no difference between AD patients with and without seizures in terms of the medications we use in the treatment of dementia. Our patients were re-

ceiving acetylcholinesterase inhibitors (rivastigmine, galantamine, and donepezil) and/or N-methyl-D-aspartate (NMDA) receptor antagonists (memantine). The use rates of acetylcholinesterase inhibitors, NMDA receptor antagonist, and a combination of acetylcholinesterase inhibitors-NMDA receptor antagonists were similar in our AD patients with and without seizures. Since our number of patients was small, subgroup comparisons were not made according to active ingredient content in those using acetylcholinesterase inhibitors.

Our study investigated the prevalence and risk factors but cannot provide a physio-pathological explanation. Recently, thoughts have come to the fore that the bi-directional relationship between AD and epileptic seizures may be related to a shared pathophysiologic process. In this context, elucidating the predictor and risk factors is important, and elucidating these relationships may be the basis for future treatment approaches.[30] The most important result in our study was the data regarding DM, IHD, and neuroleptic use. Although neuroleptic use, DM, IHD, and their medications were found at high rates in AD patients with seizures, data on neuroleptic use and IHD were evaluated as a more significant risk in the development of seizures. Although our study provides data suggesting that the use of neuroleptics and the presence of IHD or their medications facilitate the development of unprovoked generalized tonic-clonic seizures in sporadic AD, it has some limitations. The retrospective nature of our study caused us to have incomplete information about the active ingredients and doses of the drugs used and it could not be evaluated statistically. We could not comment on the high prevalence of DM and IHD in our AD patients with seizures. When these patients had a seizure, their systemic-hematological-neurological charts were reviewed and no reason that could have provoked the seizure was found. There was no information about the medications and dosages they used for DM and IHD, and we were unable to interpret our results. Despite all these limitations, we believe that these data will contribute to the organization of future studies.

Another limitation of our study is that no documentation could be made regarding focal and non-motor seizures. This issue was the most challenging point in our study. Caregivers could not recognize or detect such situations (non-motor or focal seizures). Additionally, these conditions were not a reason to visit the emergency room. Of course, it is very difficult to actually recognize focal and non-motor seizures. There is no doubt that the closest accurate information can be obtained with video-EEG when determining these seizure types. Despite this, we believe that education of caregivers can contribute significantly to determining seizure onset and seizure classifications. Our study is based on anamnesis and file records of the physicians retrospectively. Although we questioned in interviews with family members and caregivers, the most reliable results were related to tonic-clonic seizures and these seizures were documented. Although the non-provoked generalized tonic-clonic seizures recorded in our patients are witnessed, definite and undoubted, it is not certain whether they are primary or secondary. We acknowledge that there may be a lack of information regarding the onset of seizures in our study. We would like to emphasize that these limitations should be taken into consideration for research to be conducted on a similar subject.

Conflicts of Interest

There is no conflict of interest between the authors.

Ethical Approval

Ethics committee approval was given by the University of Health Sciences, Haydarpasa Numune Training and Research Hospital ethics committee on April 16, 2021 with the number of 2021/E-62977267-000-6344.

References

1. Beghi E, Giussani G. Aging and the epidemiology of epilepsy. *Neuroepidemiology* 2018;51:216-23.
2. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet* 2021;397:1577-90.
3. Toniolo S, Romoli M, Sen A. Epilepsy in older persons. *Neurol Clin* 2022;40:891-905.
4. Beagle AJ, Darwish SM, Ranasinghe KG, La AL, Karageorgiou E, Vossel KA. Relative incidence of seizures and myoclonus in Alzheimer's disease, dementia with lewy bodies, and frontotemporal dementia. *J Alzheimers Dis* 2017;60:211-23.
5. Stefanidou M, Beiser AS, Himali JJ, et al. Bi-directional association between epilepsy and dementia: the framingham heart study. *Neurology* 2020;95:e3241-7.
6. Yang F, Chen L, Yu Y, at al. Alzheimer's disease and epilepsy: an increasingly recognized comorbidity. *Front Aging Neurosci* 2022;14:940515.
7. Vossel KA, Tartaglia MC, Nygaard HB, Zeman AZ, Miller BL. Epileptic activity in Alzheimer's disease: causes and clinical relevance. *Lancet Neurol* 2017;16:311-22.
8. Palop JJ, Chin J, Roberson ED, et al. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. *Neuron* 2007;55:697-711.
9. Holth JK, Bomben VC, Reed JG, et al. Tau loss attenuates neuronal net-

work hyperexcitability in mouse and drosophila genetic models of epilepsy. *J Neurosci* 2013;33:1651-9.
10. Scarmeas N, Honig LS, Choi H, et al. Seizures in Alzheimer disease: who, when, and how common? *Arch Neurol* 2009;66:992-7.
11. Risse SC, Lampe TH, Bird TD, et al. Myoclonus, seizures, and paratonia in Alzheimer disease. *Alzheimer Dis Assoc Disord* 1990;4:217-25.
12. Hauser WA, Morris ML, Heston LL, Anderson VE. Seizures and myoclonus in patients with Alzheimer's disease. *Neurology* 1986;36:1226-30.
13. Mendez MF, Catanzaro P, Doss RC, Arguello R, Frey WH 2nd. Seizures in Alzheimer's disease: clinicopathologic study. *J Geriatr Psychiatry Neurol* 1994;7:230-3.
14. Lozsadi DA, Larner AJ. Prevalence and causes of seizures at the time of diagnosis of probable Alzheimer's disease. *Dement Geriatr Cogn Disord* 2006;22:121-4.
15. Rao SC, Dove G, Cascino GD, Petersen RC. Recurrent seizures in patients with dementia: frequency, seizure types, and treatment outcome. *Epilepsy Behav* 2009;14:118-20.
16. Bernardi S, Scaldaferri N, Vanacore N, et al. Seizures in Alzheimer's disease: a retrospective study of a cohort of outpatients. *Epileptic Disord* 2010; 12:16-21
17. Hesdorffer DC, Hauser WA, Annegers JF, Kokmen E, Rocca WA. Dementia and adult-onset unprovoked seizures. *Neurology* 1996;46:727-30.
18. Amatniek JC, Hauser WA, DelCastillo-Castaneda C, et al. Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia* 2006;47:867-72.
19. Volicer L, Smith S, Volicer BJ. Effect of seizures on progression of dementia of the Alzheimer type. *Dementia* 1995;6:258-63.
20. Romanelli MF, Morris JC, Ashkin K, Coben LA. Advanced Alzheimer's disease is a risk factor for late-onset seizures. *Arch Neurol* 1990;47:847-50.
21. Baker J, Libretto T, Henley W, Zeman A. A longitudinal study of epileptic seizures in Alzheimer's disease. *Front Neurol* 2019;10:1266.
22. Johannessen Landmark C, Henning O, Johannessen SI. Proconvulsant effects of antidepressants - what is the current evidence? *Epilepsy Behav* 2016;61:287-91.
23. Steinert T, Fröscher W. Epileptic seizures under antidepressive drug treatment: systematic review. *Pharmacopsychiatry* 2018;51:121-35.
24. Cheng CH, Liu CJ, Ou SM, et al. Incidence and risk of seizures in Alzheimer's disease: a nationwide population-based cohort study. *Epilepsy Res* 2015; 115:63-6.
25. Bloechliger M, Rüegg S, Jick SS, Meier CR, Bodmer M. Antipsychotic drug use and the risk of seizures: follow-up study with a nested case-control analysis. *CNS Drugs* 2015;29:591-603.
26. Irizarry MC, Jin S, He F, et al. Incidence of new-onset seizures in mild to moderate Alzheimer disease. *Arch Neurol* 2012;69:368-72.
27. Dunn NR, Pearce GL, Shakir SA. Adverse effects associated with the use of donepezil in general practice in England. *J Psychopharmacol* 2000; 14:406-8.
28. Hamberger MJ, Palmese CA, Scarmeas N, Weintraub D, Choi H, Hirsch LJ. A randomized, double-blind, placebo-controlled trial of donepezil to improve memory in epilepsy. *Epilepsia* 2007;48:1283-91.
29. Ha J, Son NH, Park YH, Lee E, Kim E, Jung Kim W. Association of cognitive enhancers and incident seizure risk in dementia: a population-based study. *BMC Geriatr* 2022;22:480.
30. Lu O, Kouser T, Skylar-Scott IA. Alzheimer's disease and epilepsy: shared neuropathology guides current and future treatment strategies. *Front Neurol* 2023;14:1241339.

Supplementary Material 1. Seizure inquiry form

1) Interviewer: caregiver to the patient	
Interviewer name	
Interviewer no	
Interview date	
Degree of relationship to the patient	
2) Presence of fuctuation in the patient	
Fluctuation: YES/NO	
If there is fluctuation, detailed explanation and examples	
3) Focal onset seizures	
Focal motor or sensory episodes: YES/NO	
Automatisms: YES/NO	
Olfactory/gustatory hallucinations: YES/NO	
Deja-vu: YES/NO	
Period of altered responsiveness: YES/NO	
Amnesic episodes (on waking): YES/NO	
Amnesic episodes (at other times): YES/NO	
Repetitive questioning: YES/NO	
Triggers: YES/NO	
Aura: YES/NO	
If the answer is yes to any of them, detailed explanation and examples	
4) Generalised onset seizures: YES/NO	
If the answer is yes, detailed explanation and examples	