Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-191315
IOS Press

Epilepsy in Neurodegenerative Dementias: A Clinical, Epidemiological, and EEG Study

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Accepted 27 January 2020

Abstract.

Background: Seizures are common in patients with dementia but precise epidemiologic data of epilepsy in neurodegenerative dementia is lacking.

Objective: The first aim of the study was to investigate prevalence and clinical characteristics of epilepsy in a large cohort of patients with neurodegenerative dementias. Subsequently, we explored clinical, neuropsychological, and quantitative electroencephalogram (qEEG) data of Alzheimer's disease (AD) patients with epilepsy (AD-EPI) as compared to AD patients without epilepsy (AD-CTR).

Methods: We retrospectively evaluated consecutive patients with a diagnosis of a neurodegenerative dementia and a clinically diagnosed epilepsy that required antiepileptic drugs (AED). All patients underwent baseline comprehensive neuropsychological assessment. A follow-up of at least one year was requested to confirm the dementia diagnosis. In AD patients, qEEG power band analysis was performed. AD-CTR and AD-EPI patients were matched for age, Mini-Mental State Examination score, and gender.

Results: Thirty-eight out of 2,054 neurodegenerative dementia patients had epilepsy requiring AED. The prevalence of epilepsy was 1.82% for AD, 1.28% for the behavioral variant of frontotemporal dementia (bvFTD), 2.47% for dementia with Lewy bodies (DLB), and 12% for primary progressive aphasia. Epilepsy were more drug-responsive in AD than in non-AD dementias. Finally, no significant differences were found in neuropsychological and qEEG data between AD-EPI and AD-CTR patients.

Conclusion: In our cohort, AD, FTD, and DLB dementias have similar prevalence of epilepsy, even if AD patients were more responsive to AED. Moreover, AD-EPI patients did not have significant clinical, neuropsychological qEEG differences compared with AD-CTR patients.

Keywords: Alzheimer's disease, dementia, EEG, epilepsy, seizure

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INTRODUCTION

Although it is known that demented patients are more prone to present seizures than subjects without dementia [1, 2], precise epidemiologic data of epilepsy in dementia is lacking [1] and, on

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the other hand, it is known that old people with epilepsy are at increased risk of cognitive decline [3], as cognitive impairment across all domains has actually been reported in these patients [4]. Overall, cognitive decline over time in people with epilepsy is faster compared to aging-related cognitive decline in subjects without epilepsy [5]. Furthermore, a bidirectional relationship between epilepsy and dementia has been suggested [3]. Thus, the concept of an accelerated cognitive aging in patients with epilepsy has been suggested [5], but it is still unknown whether dementia worsens more rapidly in demented patients with epilepsy compared to those without.

Gowers first introduced the concept of epileptic dementia, implying that in some subjects dementia and epilepsy may be the consequence of the same underlying disorder [6]. The association between vascular dementia and epilepsy is common [7]. Neurodegenerative dementias as well may develop seizures. Alzheimer's disease (AD) is the most frequent cause of dementia and is frequently associated with epilepsy [8], but non-AD dementia patients may also have epilepsy [9]. However, most of the published studies investigating the association between dementia and epilepsy did not evaluate the causes of dementia. Moreover, neurophysiological and neuropsychological features of dementia patients with dementia epilepsy are lacking.

This study has two aims: 1) to investigate the prevalence and the clinical characteristics of epilepsy in a large cohort of patients with neurodegenerative dementias; and 2) to explore clinical, neuropsychological, and electroencephalogram (EEG) data of AD patients with epilepsy as compared to AD patients without epilepsy.

METHODS

Subjects

We retrospectively evaluated consecutive patients admitted to our University Hospital memory clinic between January 1999 and December 2016. The main inclusion criteria were 1) a diagnosis of neurodegenerative dementia and 2) the presence of seizures under antiepileptic drug (AED) treatment with an onset close to the time of dementia diagnosis or later on during the follow-up.

The patients underwent a baseline clinical assessment including neurological examination and neuropsychological evaluation. They underwent brain magnetic resonance imaging (MRI), or computed tomography in the case MRI was unfeasible. They also underwent ambulatory scalp EEG during relaxed wakefulness. When the clinical diagnosis was uncertain, patients underwent brain radionuclide imaging, including brain perfusion ^{99m}Tc-ECD single photon emission tomography (SPECT) or brain metabolism ^{18}F-FDG positron emission tomography (PET).

The main exclusion criteria were 1) a remote history of epilepsy (defined as seizure onset at least 5 years prior to cognitive symptoms [2]) and 2) a history of stroke and/or a diagnosis of vascular dementia [10], including mixed neurodegenerative/vascular dementia, with cortical/iuxtacortical infarcts.

The diagnosis of neurodegenerative dementia was made according to the following criteria:

- AD: according to the 1984 NINCDS-ADRDA Alzheimer's Criteria [11] for patients diagnosed between 1999 and 2011, and according to the 2011 NIA-AA criteria [12] for patients diagnosed from 2011.
- Frontotemporal dementia (FTD): according to the 1998 criteria [13] for patients diagnosed from 1999 to 2011, after 2011 the criteria for behavioral variant FTD (bvFTD) were used [14].
- Dementia with Lewy bodies (DLB): according to the 1996 criteria [15] for patients diagnosed from 1999 to 2005, and according to the 2005 criteria of the international consortium on the DLB [16] for patients from 2005.
- Parkinson's disease dementia (PDD): according to the Movement Disorder Society criteria [17].
- Primary progressive aphasia (PPA): according to the 1987 criteria [18] for patients diagnosed from 1999 to 2011, and according to the 2011 criteria [19] for patients from 2011.
- Posterior cortical atrophy (PCA): according to the criteria of Benson and collaborators of 1988 [20].

The patients underwent six month-based clinical follow-up after the baseline assessment. A follow-up of at least one year was requested to confirm the diagnosis.

For each patient, a case report form (CRF) was created, including age, gender, years of education, type of dementia diagnosis, the onset of seizures (before, after or concomitant with the diagnosis of dementia), and the type of seizure at onset (focal, generalized or unknown), seizure type classification basic version [24], AED treatment and the response to therapy (seizure-free, improved, and not improved).

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Patients were considered improved by therapy when an improvement in either frequency or intensity of seizures was judged clinically significant by the neurologist.

The study protocol met the approval of the local Ethics Committee, and all participants signed an informed consent form in compliance with the Helsinki Declaration of 1975.

Neuropsychological evaluation

The following neuropsychological evaluation was performed at baseline: 1) categorical and phonological verbal fluency to asses language [21]; 2) Trail-Making Test (TMT) A [22], Stroop color-word test [23], and digit span [24] to evaluate attention and working memory; 3) TMT B [22], Stroop color test [23], and symbol-digit [25] for executive functions; 4) Clock Drawing Test (CDT) [26] and figure copying of the mental deterioration battery (simple copy and copy with guiding landmarks) [27] for visuospatial capabilities; and 5) Rey auditory learning verbal test [28] (RALVT, immediate and delayed recall) and Corsi's block design [29] to investigate memory.

The Mini-Mental State Examination (MMSE) [30] was performed as a general measure of cognitive functioning. The Geriatric Depression Scale (GDS) [31] was used to investigate the presence of depression.

EEG recording and data processing

EEG recordings were obtained from patients seated in a recliner with eyes closed. EEG electrodes were placed using standard 10–20 EEG electrode positions: Fp2, F4, Fp1, F3, and Fpz (frontal); F8, T4, T6, F7, T3, and T5 (temporal); C4 P4, C3, P3, PZ, and CZ (centro-parietal); O2 and O1 (occipital). Recordings were referenced to the Fpz electrode, Oz electrode served as ground. EEG was recorded with a sampling rate of 256 Hz, at a bandpass filter of 0.5–70 Hz.

EEG data were manually analyzed off-line to reject artifacts. One minute of artifact-free EEG data was re-referenced to common average for further analysis. Quantitative EEG (qEEG) power spectrum was calculated with the Fourier Transform (Welch method), applied to 2-s segments with 2-s overlap (Tukey window), for each brain area (i.e., frontal, temporal, centro-parietal, and occipital). The EEG spectrum was then divided into the following frequency bands: delta (2.10–4 Hz), theta (4.10–8 Hz), alpha (8.10–12 Hz), sigma (12.10–16 Hz), and beta (16.10–24 Hz) and relative power was computed for each band as normalized to the total EEG power. In order to evaluate EEG power distribution in a large band (2–16 Hz), the power-weighted mean frequency (MF) was calculated for each brain area.

Statistical analysis

The first analysis was aimed at evaluating the relationship between epilepsy and the different types of neurodegenerative dementia. The prevalence of epilepsy was calculated for each type of neurodegenerative dementia. Then, a logistic regression was performed, using the diagnosis of neurodegenerative dementia as the dependent variable (categorical variable) and the characteristics of epilepsy included in the CRF, as detailed before, were the independent variables.

The second analysis was aimed at comparing clinical features, neuropsychological tests scores and qEEG data of subjects suffering from AD and epilepsy (AD-EPI) with subjects suffering from AD, without epilepsy (AD-CTR). The two groups were matched for age, MMSE score, and gender. Continuous variables were analyzed by unpaired *t* test and categorical variables with the chi-square test.

RESULTS

Epilepsy and neurodegenerative dementias

From 1996 to 2016, we found in our clinical database 2,054 patients with diagnosis of neurodegenerative dementia (Supplementary Figure 1). 1,645 were AD (80.09%), 235 bvFTD (11.44%), 81 DLB (3.94%), 64 PDD (3.12%), 25 PPA (1.2%), and 4 PCA (0.19%).

Among these patients, 38 (1.85%) were affected by epilepsy (Fig. 1). Among these, 30 were diagnosed with AD (78.95%), 3 had bvFTD (7.89%), 3 PPA (7.89%), and 2 DLB (5.26%).

Large epidemiology studies have shown that the prevalence of epilepsy in the elderly ranged from 0.5 % [9] to 0.97 % [2]. In our cohort of neurodegenerative dementias, prevalence of epilepsy is significantly higher compared to literature data of epilepsy in the elderly ($p < 0.001$, Fisher Exact Test).

In our cohort of neurodegenerative dementias, the prevalence of epilepsy was 1.82% for AD, 1.28% for bvFTD, 2.47% for DLB, and 12% for PPA (Supple-

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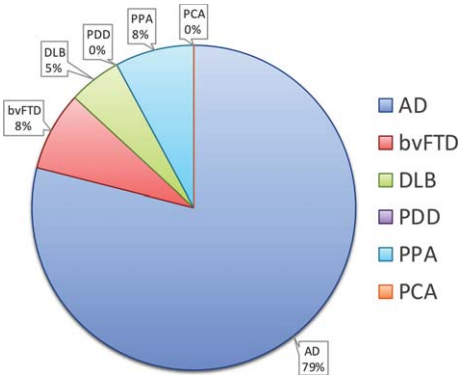

Fig. 1. Distribution of neurodegenerative dementias in the study group of dementia patients with concomitant epilepsy. AD, Alzheimer's disease; DLB, dementia with Lewy Bodies; bvFTD, fronto-temporal dementia, behavioral variant; PPA, primary progressive aphasia.

mentary Figure 2). The characteristics of epileptic seizures are shown in Table 1.

Logistic regression showed a significant correlation ($p < 0.0001$) between dementia and treatment response. In particular, 23 patients with AD (76.7%) were seizure free after using AEDs.

Epilepsy and Alzheimer's disease

Eight patients in the AD-EPI group had an EEG with insufficient quality to perform qEEG analysis, thus 22 AD-EPI patients were considered for subsequent analysis. Main clinical and demographic data of AD patients with and without epilepsy are summarized in Table 2. Per selection criteria of AD patients without epilepsy that were chosen so as to be age and severity-matched with those with epilepsy, no statistically significant difference was found between the two groups.

Neuropsychological tests score of AD patients with and without epilepsy are shown in Table 3. Considering that the two groups were matched for age, gender, education, and MMSE, raw neuropsychological data were used. No statistically significant difference was found between the two groups.

QEEG data of AD patients with and without epilepsy are shown in Table 4. AD-EPI group showed higher relative power values in the sigma band compared with the AD-CTR group, which however did not survive to Bonferroni's correction for multiple comparisons.

DISCUSSION

In the present study, we evaluated a large cohort of consecutive outpatients admitted to our university memory clinic from 1999 to 2016. We selected patients who received a diagnosis of neurodegenerative dementia and who also were suffering from epilepsy. We exclude patients who had a remote onset of epilepsy, in order to investigate the possible relationship between the onset of epilepsy and the neurodegenerative process underlying dementia.

The first result is that the prevalence of epilepsy was similar for AD, bvFTD, and DLB dementias. Instead, PPA patients showed higher prevalence of epilepsy. However, this result must be interpreted with caution, considering the limited number of PPA

Table 1
Characteristics of epileptic seizures in patients affected by neurodegenerative dementias. For age, mean values ± standard deviation are shown

	Total	AD	bvFTD	DLB	PPA
	38	30	3	2	3
Age	72.7 ± 7.7	71.9 ± 8.0	71.3 ± 5.5	67.0 ± 7.1	67.3 ± 4.5
Epilepsy Onset					
-After Dementia diagnosis	21 (55.3%)	15	1	2	3
-Before Dementia diagnosis	7 (18.4%)	5	2	0	0
-Concomitant with Dementia diagnosis	7 (18.4%)	7	0	0	0
-Unknown	3 (7.9%)	3	0	0	0
Seizures type at onset					
-Generalized	17 (44.7%)	15	1	1	0
-Focal	15 (39.5%)	10	1	1	3
-Unknown	6 (15.79%)	5	1	0	0
Treatment Response					
-Seizure Free	24 (63.2%)	23	0	0	1
-Improved	3 (7.9%)	0	2	1	0
-Not Improved	11 (28.9%)	7	1	1	2

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; bvFTD, frontotemporal dementia, behavioral variant; PPA, primary progressive aphasia.

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Table 2
Main clinical and demographic data in subjects with dementia due to AD and epilepsy (AD-EPI) and subjects with dementia due to AD without epilepsy (AD-CTR). Mean values ± standard deviation (range) are shown

	AD-EPI	AD-CTR	p
N	22	22	
Age, y	71.95 ± 8.00 (57–90)	72.27 ± 6.85 (54–82)	n.s.
Gender	26F/4M	17F/5M	n.s.
Education, y	7.41 ± 4.06 (0–17)	9.45 ± 4.60 (2–17)	n.s.
MMSE	24.14 ± 4.36 (10–30)	23.95 ± 3.64 (15–30)	n.s.
GDS	5.05 ± 3.22 (0–12)	5.14 ± 3.09 (2–15)	n.s.
AChE-inhibitors	11 (50%)	4 (23%)	n.s.
Hypertension	16 (73%)	10 (46%)	n.s.
Diabetes	3 (14%)	2 (9%)	n.s.
Heart disease	6 (27%)	7 (32%)	n.s.
Hypercholesterolemia	12 (54%)	11 (50%)	n.s.
Follow-up, mo	54.0 ± 34.0 (8–118)	50.8 ± 30.7 (5–124)	n.s.
Follow-up MMSE	13.8 ± 7.7 (4–30)	11.4 ± 8.27 (1–28)	n.s.

AChE-inhibitors, acetylcholinesterase inhibitors; F, female; GDS, Geriatric depression scale; M, male; MMSE, Mini-Mental State Examination; n.s., not significant.

Table 3
Neuropsychological tests raw scores in subjects with dementia due to Alzheimer's disease and epilepsy (AD-EPI) and subjects with dementia due to Alzheimer's disease without epilepsy (AD-CTR). Mean values ± standard deviation (range) are shown

	AD-EPI	AD-CTR	p
TMT A (s)	125.94 ± 95.37 (29–350)	112.63 ± 71.95 (41–300)	n.s.
TMT B (s)	362.44 ± 171.54 (88–533)	343 ± 180.51 (89–533)	n.s.
Symbol-digit	16.00 ± 11.87 (1–42)	16.50 ± 9.55 (1–34)	n.s.
Stroop Color	29.06 ± 6.52 (18–45)	28.94 ± 8.74 (9–43)	n.s.
Stroop Color-word	10.74 ± 6.06 (1–21)	8.13 ± 4.90 (3–17)	n.s.
Corsi's Span	3.29 ± 1.36 (0–5)	3.73 ± 1.22 (2–6)	n.s.
Digit's Span	5.76 ± 2.56 (3–15)	4.87 ± 0.64 (4–6)	n.s.
RALVT immediate	23.35 ± 9.96 (6–49)	19.89 ± 6.91 (11–34)	n.s.
RALVT delayed	2.40 ± 2.68 (0–7)	2.16 ± 2.57 (0–9)	n.s.
CDT	3.83 ± 3.15 (0–7)	4.41 ± 3.02 (0–7)	n.s.
Figure copying, simple copy	6.95 ± 2.22 (2–10)	7.57 ± 2.31 (3–12)	n.s.
Figure copying, with guiding landmarks	56.21 ± 12.58 (24–68)	59.05 ± 9.75 (38–70)	n.s.
Categorical verbal fluency	13.0 ± 5.03 (2–23)	12.93 ± 3.83 (8–21)	n.s.
Phonological verbal fluency	24.30 ± 9.81 (0–39)	20.14 ± 9.65 (10–49)	n.s.

CDT, Clock drawing test; n.s., not significant; RALVT, Rey Auditory Learning Verbal Test; TMT, Trail Making Test.

subjects in our sample, which is notoriously rare [19]. The second result is the statistically significant association between the response to AED and the diagnosis of neurodegenerative dementia. In particular, among the various type of dementias, patients with AD showed a better response to AED therapy. However, it has to be noted that the other groups were smaller than the AD group, thus this result also must be taken with caution.

AD is the most common neurodegenerative dementia [32]. Growing literature data are suggesting the association between brain amyloidosis and epilepsy [8, 33]. Indeed, seizures can also precede cognitive symptoms in AD patients [34]. In agreement with literature data, in our cohort AD is the most common cause of degenerative dementia and it is also the most common cause of dementia in the group of patients with neurodegenerative dementias and concomitant epilepsy. However, in our study the prevalence of epilepsy of other common neurodegenerative dementias (FTD and DLB) is at least comparable with AD.

Few studies have investigated epilepsy in non-AD neurodegenerative dementias. A recent epidemiological study in the United States showed that AD dementia had a higher risk of developing seizures and epilepsy compared with non-AD dementias [9]. However, in that study all non-AD dementias were considered, including vascular and other secondary dementias. Moreover, it was a study based on an

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Table 4
qEEG data in subjects with dementia due to AD and epilepsy (AD-EPI) and subjects with dementia due to AD without epilepsy (AD-CTR). Mean values ± standard deviation (range) are shown

	AD-EPI	AD-CTR	*p*
Relative bandpower			
DELTA (2.10–4 Hz)			
-Frontal	7.73 ± 3.16	7.59 ± 3.84	n.s.
-Temporal	8.81 ± 4.10	7.59 ± 2.89	n.s.
-Centro/Parietal	7.72 ± 3.29	7.30 ± 3.32	n.s.
-Occipital	6.50 ± 3.05	6.87 ± 3.61	n.s.
THETA (4.10–8 Hz)			
-Frontal	18.93 ± 8.66	18.35 ± 9.66	n.s.
-Temporal	20.92 ± 9.65	19.90 ± 9.89	n.s.
-Centro/Parietal	19.77 ± 8.99	19.31 ± 9.35	n.s.
-Occipital	17.48 ± 8.27	19.20 ± 10.04	n.s.
ALPHA (8.10–12 Hz)			
-Frontal	20.17 ± 11.72	17.55 ± 9.14	n.s.
-Temporal	20.73 ± 9.08	18.95 ± 8.39	n.s.
-Centro/Parietal	25.82 ± 12.28	24.59 ± 11.57	n.s.
-Occipital	32.39 ± 19.88	28.73 ± 15.00	n.s.
SIGMA (12.10–16 Hz)			
-Frontal	6.29 ± 2.70	4.69 ± 2.57	0.033*
-Temporal	6.61 ± 2.23	5.21 ± 2.34	0.034*
-Centro/Parietal	8.97 ± 3.78	6.72 ± 2.99	0.023*
-Occipital	6.88 ± 2.66	5.73 ± 2.73	n.s.
BETA (16.10–24 Hz)			
-Frontal	8.03 ± 2.90	7.59 ± 5.04	n.s.
-Temporal	7.23 ± 2.57	6.89 ± 3.21	n.s.
-Centro/Parietal	9.59 ± 3.58	8.59 ± 4.25	n.s.
-Occipital	6.49 ± 2.87	6.42 ± 3.21	n.s.
Mean frequency			
-Frontal	11.14 ± 1.44	10.82 ± 1.66	n.s.
-Temporal	10.96 ± 1.22	10.74 ± 1.19	n.s.
-Centro/Parietal	9.72 ± 1.05	9.45 ± 1.02	n.s.
-Occipital	10.68 ± 1.41	10.62 ± 1.14	n.s.

*Not surviving Bonferroni's correction for multiple comparison.

administrative database, thus it was unknown whether the epilepsy was of new or remote onset. Another recent study was aimed at evaluating the relative incidence of seizures in neurodegenerative dementias [35] showing that the cumulative probability of developing seizures after dementia onset was higher in AD and DLB compared with FTD. It has to be noted that FTD patients have shorter life expectancy than non-FTD dementias and this may contribute to their lower cumulative probability of seizures. However, that study was aimed at identifying the incidence of seizures, but it is not known whether the patients further develop epilepsy that needed antiepileptic treatment. According to international criteria, a single seizure is not enough to make epilepsy diagnosis [36], unless a chronic predisposing factor for developing successive seizures may be demonstrated. Indeed, several causes of provoked seizures has been described, especially in the elderly [37]. In the present study, we selected only those patients who were diagnosed as having epilepsy, with causes of provoked seizures being excluded, and therefore underwent antiepileptic treatment. This is because we believe that this approach would increase the probability that the pathophysiology of seizures in the evaluated patients is directly related to the pathophysiology of neurodegenerative dementias. With this specific study design, we found that the prevalence of definite epilepsy that requested antiepileptic treatment is similar for AD and non-AD neurodegenerative dementias and it is lower range with respect to the reported prevalence of seizures in literature studies, which ranges from 0.5 to 64% [38]. However, the largest epidemiological study conducted so far on more than 3 million AD patients found a seizure prevalence of 1.43% [9], thus very close to the prevalence in the present study. Moreover, the weighted average prevalence of epilepsy in AD, according to literature data [38], is 1.5%. A recent study [39] found an epilepsy prevalence of 25.7% in a cohort of patients with dementia or mild cognitive impairment. However, this study has several methodological discrepancies in comparison with our, including the presence of vascular dementia and the inclusion of patients with clinical suspect of epilepsy, but without anti-epileptic treatment. If the same criteria used in our study are applied to Baker et al dataset, the epilepsy prevalence would decrease to 2.1 %, thus comparable to our result.

The underlying mechanism of epileptogenesis in neurodegenerative dementias is thought to be related to an increased cortical excitability due to cortical deposition/aggregation of pathological proteins. In AD, network hyperexcitability has been related to aberrant network activity due to amyloid-β [33]. However, both increased seizure susceptibility and aberrant network excitability have been related to the overexpression of both tau protein and α-synuclein in animal models of FTD [40] and DLB [41]. Thus, the precise cause of epileptic seizures in patients with neurodegenerative dementias has not been fully elucidated yet, and it is likely underlined by complex mechanism and heterogeneous neuropathology. For instance, it has been proposed that both amyloid-β and tau protein abnormalities must be present to produce aberrant excitatory activity that results in epileptic seizures [42]. Moreover, in non-demented patients suffering from refractory temporal lobe epilepsy, the presence of tau pathology has been related cognitive decline [43]. Thus, the role of tau protein seems relevant in determining the increased risk of epilepsy [44]. Indeed, tau pathology is present

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in AD, but it may also be present in FTD and DLB [44]. The results of the present study seem to suggest a preponderant role of tau protein among all misfolded ones. Indeed, combining PDD and DLB, where α-synuclein is invariable and amyloid-β very common, the frequency of epilepsy is extremely low (approximately 0.7%), while the highest frequency has been observed in PPA, of which the non-fluent type is mainly related to tau deposition. This is in agreement with recent literature data highlighting the role of tau protein in increasing seizure susceptibility and aberrant network excitability [4, 44].

A novel finding of the present study is that epilepsy in AD dementia seems to be more drug-responsive than epilepsy in non-AD dementias. As discussed before, this result must be taken with caution considering the limited number of subjects. Nevertheless, considering that AD is the most frequent cause of neurodegenerative dementia, we performed a second analysis aimed at evaluating whether patients with AD and epilepsy (AD-EPI) had different clinical, neuropsychological and EEG characteristics compared with patients with AD without epilepsy (AD-CTR). The two groups were matched for age, education, and MMSE score in order to evaluate the real effect of epilepsy on such patients. No significant differences were found in neuropsychological and qEEG data between the two groups. AD-EPI patients tended to have higher values of relative power in the sigma band (12.10–16 Hz) in several brain regions, without surviving Bonferroni's correction for multiple comparison. This finding could have different interpretations. The first hypothesis is that the increase in the sigma band may be an expression of an increased neuronal excitability due to epileptic pathology in AD-EPI subjects. The statistical significance may not be achieved because of the relatively limited number of subjects. The second, more likely, hypothesis is that the increase of rapid EEG frequencies is due to the chronic effect of AED therapy.

Several literature data showed the effect of AED on qEEG data. For example, "old generation" AEDs (such as phenytoin, carbamazepine and phenobarbital) tend to increase the relative power of slow bands [45–47]. On the other hand, "new generation" AEDs (such as levetiracetam and lamotrigine) tend to increase the relative power of the fast bands [48, 49]. Unfortunately, in our study, considering the limited number of subjects, it was not possible to make a more detailed analysis of this phenomenon. However, in the AD-EPI group, about half (12/25) of the subjects took levetiracetam while the remainder took "old generation" AEDs.

The qEEG can be considered an indirect marker of neurodegeneration in AD [50]. In our study, the qEEG data were found to be substantially overlapping between AD-EPI and AD-CTR patients while, as a descriptive finding, interictal epileptiform discharges were more likely found in the AD-EPI group. Furthermore, the two study groups did not show statistically significant difference in cognitive test performance. Therefore, although previous studies have reported an association between epilepsy and amyloidosis in AD [8, 33], in the present study subjects with concomitant AD and epilepsy did not have a more severe clinical phenotype or a more sever neurodegeneration, measured indirectly with the EEG. Indeed, clinical studies have reported only a moderate correlation between cerebral amyloidosis markers and neurodegeneration markers in AD [51–53]. The clinical significate of this result remains to be investigated through the study of amyloidosis and neurodegeneration markers.

As a descriptive finding, the presence of seizures was perceived as a major clinical problem by patients and caregivers, especially those with seizures with motor component. Besides that, no clinically relevant association with concomitant medications, comorbidities or rate of worsening during the clinical follow-up was found. In particular, AD-EPI did not have a worse cognitive outcome compared with AD-CTR patients, thus suggesting that the presence of epilepsy does not significantly interfere with the clinical course of the disease.

The present study has some limitations. The first is that the data were collected retrospectively. However, the data were collected homogeneously over the years by the same researchers and with standardized diagnostic procedures. Nevertheless, the retrospective nature of the study may have led to a slight underestimation of the epilepsy prevalence in our study. The second limit is the lack of biomarkers for brain amyloidosis and tau protein. Unfortunately, for most patients this marker was not available in our center yet, considering that the study period is from 1999 to 2016. Third, non-AD dementias were less represented than AD in our sample, thus larger studies are needed to draw definite conclusions.

In conclusion, we have found that in our cohort of neurodegenerative dementia, AD, FTD, and DLB dementias have similar prevalence of epilepsy, even if AD patients were more responsive to antiepileptic treatment. Moreover, AD patients with epilepsy did not have significant clinical, neuropsychological of

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qEEG differences compared with AD patients without epilepsy. Larger studies are needed to confirm these findings.

DISCLOSURE STATEMENT

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-1315r1).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-191315.

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