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Seizures in Alzheimer's disease: a retrospective study of a cohort of outpatients

Silvia Bernardi, Nicola Scaldaferri, Nicola Vanacore, Alessandro Trebbastoni, Ada Francia, Aurelio D'Amico, Massimiliano Prencipe

Department of Neuroscience, "Sapienza" University of Rome, Italy

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ABSTRACT – *Purpose*. The aim of our study was to define the frequency of seizures in a population of outpatients attending a cognitive function clinic in Italy and to identify risk factors for seizures in patients with Alzheimer's disease. *Methods*. In this retrospective study, we analyzed our clinical records to gather information on patients' demographic, metabolic, cardiovascular and cognitive features. We sought to determine the significance of abnormal neuroimaging findings and the use of potentially epileptogenic drugs on the onset of seizures. From the records of 583 patients referred to the clinic for cognitive disturbances, we identified 145 patients with Alzheimer's disease. *Results*. Of these 145 patients, 14 (9.7%) had a history of complex partial or generalised seizures, or both. Of the risk factors identified, onset of seizures was associated with male gender and none of the patients with seizures had diabetes. The risk of seizure onset was higher in Alzheimer's disease patients with hyperlipaemia and severe dementia. No other risk factors were identified, although hypertensive patients seemed to be protected. *Conclusions*. Seizures in Alzheimer's disease are frequent and often under-recognized. In elderly patients, especially those with Alzheimer's disease, correct diagnosis and treatment are important to prevent disease from worsening and disability from increasing. Patients with dementia should routinely undergo history-taking designed to elicit a history of seizures and define patients at high risk.

Key words: seizures, Alzheimer, dementia, risk factor, hyperlipaemia

Dementia is a major risk factor for seizures in the elderly (Hersdoffer *et al.*, 1996; Forsgren *et al.*, 1996; Hommet *et al.*, 2008; Mendez and Lim, 2003). Epileptic seizures may contribute to the natural history of Alzheimer's disease (AD) (McKhann *et al.*, 1984) and detecting seizures is essential to predicting outcome and preventing seizure-related adverse events (Volicer *et al.*, 1995; Hommet *et al.*, 2008). The risk of seizures developing is 6-10 times greater in patients with AD than in healthy elderly persons of similar age (Hersdoffer *et al.*, 1996; Hauser *et al.*, 1986).

To our knowledge, no previous studies have estimated the frequency of epileptic seizures in AD in an outpatient population in Italy. Moreover, there is a lack of information regarding cardiovascular and metabolic events and medications that may constitute clinical risk factors for seizures in patients with AD.

Correspondence:
Dr N. Scaldaferri
Dipartimento Scienze Neurologiche,
Viale Università, 30,
00185 Roma, Italy
<nscaldaferri@libero.it>

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Our aim in this retrospective study was to assess the frequency of seizures in outpatients attending a cognitive function clinic in our university hospital and to identify possible risk factors for seizure onset. To do so, we reviewed our patients' clinical records and gathered data on age, education, cognitive decline, and gender. We especially sought to identify any influence of potentially treatable cardiovascular factors, and antipsychotic and antidepressant drugs which may promote epileptic seizures.

Cohort population

After retrospectively searching the clinical records of all patients referred to the cognitive function clinic in our university hospital in Rome, we identified 583 patients seen for the first time who underwent at least two clinical diagnostic assessments between January 2001 and December 2006. All patients' records provided data on a medical and neurological diagnostic work-up by neurologists specialized in cognitive disturbances. The work-up included laboratory screening, axial computerized tomography (CT) scanning or nuclear magnetic resonance imaging (MRI) of the brain. Cognitive and functional data recorded included Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR) scale and a full neuropsychological battery. The records were also examined for data on concomitant medical conditions such as diabetes, hypertension and hyperlipaemia. According to the records, all diabetic patients received oral or subcutaneous antidiabetic therapy. Hypertensive patients were prescribed antihypertensive drugs to maintain systolic and diastolic blood pressure values of < 140/80 mmHg. Patients with hyperlipaemia (> 240 mg/L) were prescribed statins. Clinical data included information on administered neurological therapy (anti-dementia, antidepressant and antipsychotic agents).

Of the 583 new patients examined, 245 (42%) received a diagnosis of dementia, 105 (18%) showed "mild cognitive impairment", according to the Petersen criteria (Petersen *et al.*, 2001), and 235 (40%) manifested no signs of cognitive impairment. Of the 245 demented patients, our study identified 145 (59%) subjects who met the criteria for AD (McKhann *et al.*, 1984), 47 (19%) for vascular dementia (Tris Oman *et al.*, 1993) and 53 (22%) for other types of dementia *(figure 1)*. The mean age of the 145 patients with AD was 78.0 ± 7.2 years (range: 51-91). There

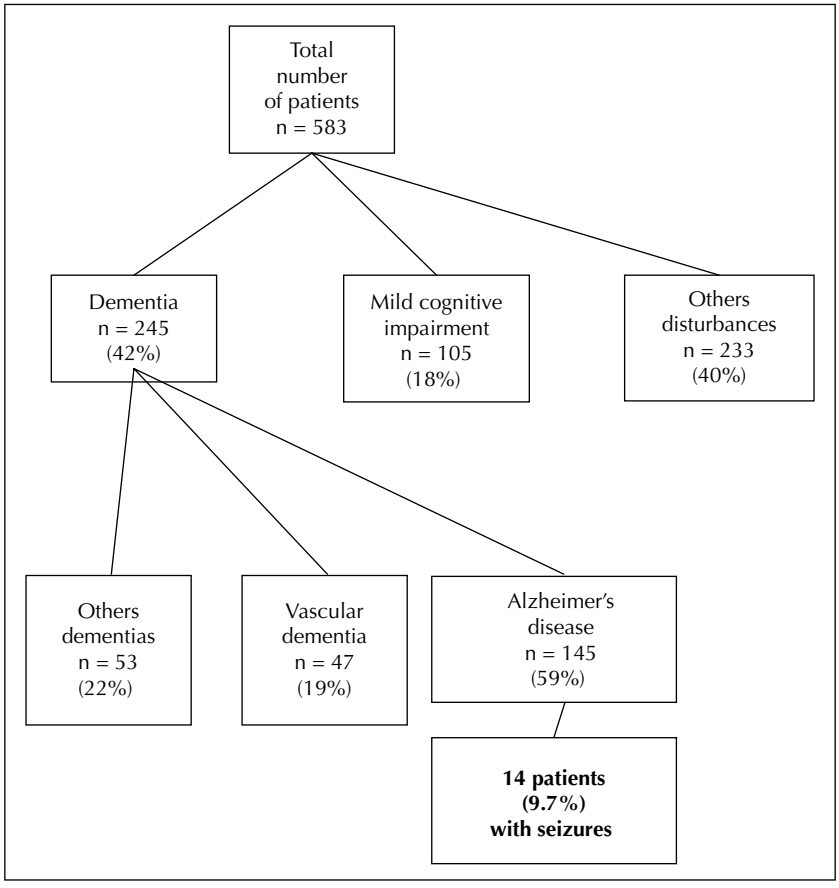

Figure 1. Population recorded and diagnosed between January 2001 and December 2006.

were 89 women (61.4%) and 56 men (38.6%). Mean number of years of education was 6.7 ± 4.2 (0-17); mean time (years) from reported onset of cognitive symptoms to last observation was 5.3 ± 2.2 (2-14), and the mean Mini Mental State Examination (MMSE) score was 19.9 ± 6.3 (3-27). According to the Clinical Dementia Rating (CDR) scale, 45 patients (31%) had mild dementia, 76 (52.4%) moderate dementia and 24 (16.6%) severe dementia. Of the 145 AD patients whose reports were reviewed, 21 had undergone electroencephalographic (EEG) recording. All patients for whom seizures were reported had an EEG recording over the three months following the attacks.

Methods

To identify possible risk factors for the onset of epileptic seizures we analyzed the following data: number of years from reported onset of cognitive symptoms, severity of disease at entry (grouped according to the CDR ≤ 2 and 3) and metabolic and cardiovascular risk factors such as diabetes, hyperlipaemia, and hypertension. We considered CT and MRI brain scans, classifying them as normal, with atrophy, lacunar or multi-infarct encephalopathy, or both abnormalities. We collected data at the last visit for administered therapy that included anti-cholinesterase-inhibitors (AChE-I) and memantine, antidepressants (serotonin-reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants), and antipsychotic agents. All data were collected by neurologists with expertise in dementia and were reviewed by a physician from the epileptic centre at our department. Seizures were diagnosed according to the Commission on Classification and Terminology of ILAE (International League Against Epilepsy, 1981). Patients with seizures underwent full haematological screening, EEG recording and MRI or CT brain scans to exclude symptomatic seizures.

Statistical analysis

Unless otherwise specified, all values in the text are expressed as mean ± SD. P-values equal to or less than 0.05 were considered statistically significant. Odds ratios (OR) and relative 95% confidence intervals (CI) were estimated for categorical variables.

Results

In the cohort of 145 patients with AD, our study identified 14 patients (9.7%) whose records referred to seizures *(figure 1)*. The frequency of seizures was three times higher in men than in women *(table 1)*. Of the 145 patients with AD whose records we reviewed, 13 had partial complex seizures with secondary generalisation and one patient reportedly had generalised attacks. All patients' seizures were unprovoked. For most patients with partial complex seizures the informant reported initial motor signs including head version or oral automatisms and loss of consciousness, followed by tonic-clonic seizures. All patients' reports referred to a prolonged confused state after the episode. The reports for 10 of the 14 patients with seizures (71.4%) described two or more attacks. None of the records mentioned a family history of epilepsy or a history of seizures before the onset of cognitive disturbances. The mean time period that elapsed between the diagnosis of AD in our centre and the reported onset of seizures was 3.6 ± 1.6 years. All patients diagnosed with seizures were treated with antiepileptic drugs.

No difference in age, education or disease duration (the reported onset of cognitive disturbances) was observed between the groups with and without seizures *(table 1)*. No association was found between seizure onset and severity of dementia, although the percentage of patients with seizures was almost twice as high in the group with more severe dementia (CDR = 3) than in the other groups (28.6% *vs* 15.3%) *(table 1)*.

Although the analysis of cardiovascular risk factors did not identify any correlation with hypertension or dyslipidaemia, the percentage of hypertensive patients was almost twice as high in the group without seizures relative to those with seizures (47.3% *vs* 28.6%). In contrast, the percentage of dyslipidaemic patients was almost twice as high in the group of patients with seizures relative to those without (21% *vs* 13%) *(table 1)*. No patients with seizures had diabetes.

No correlation was found between neuroimaging findings (atrophy vascular encephalopathy or both) and seizure onset or between psychotropic drugs, anti-dementia therapy and presence of seizures *(table 1)*.

In the few patients whose records included EEG recordings, EEG abnormalities were almost twice as frequent in the seizure group than the seizure-free group. EEG recordings in the 14 patients with seizures showed abnormalities in 12 patients (85.7%); seven (50%) patients' recordings showed non-specified slowing, five (35.7%) had spike/waves and two (14.3%) showed normal EEG patterns. In the seizure-free group, four patients (57.1%) had normal EEGs and three (42.9%) abnormal EEGs, with non-specific slowing.

Discussion

In this retrospective, record-based study of patients with AD attending a university cognitive function clinic between 2001 and 2006, a 9.7% frequency of epileptic seizures was observed. In this study sample, seizures were more frequent in men than in women. The frequency of seizures

Table 1. Analysis of risk factors for seizure onset in the population of patients with Alzheimer's disease.

Risk factors	Patients with seizures (n = 14)	Patients without seizures (n = 131)	P-value or OR (CI 95%)
Sex M/F	9/5	47/84	3.22 (1.0-10.2)
Age (in years)	77.9 ± 8.3	77.8 ± 7.2	ns
Education (in years)	8.3 ± 4.3	6.6 ± 4.2	ns
Disease duration[a] (in years)	5.8 ± 1.1	5.3 ± 2.3	ns
Clinical dementia rating 3 *vs* 1/2[b]	4/10	20/111	2.2 (0.5-7.6)
Hypertension Y/N	4/10	62/69	0.4 (0.1-1.4)
Diabetes Y/N	0/14	34/97	0.03
Dislipidemia Y/N	3/11	17/114	1.82 (0.5-7.2)
Neuroimaging findings			ns
- normal	1	9	
- atrophy	5	41	
- vascular lesions	1	12	
- atrophy + vascular lesions	7	69	
Antidementia therapy			ns
- no therapy	0	2	
- memantine	0	9	
- AChE-I	13	111	
- both	1	9	
Antidepressant therapy			ns
- SSRIs	6	81	
- tricyclic antidepressants	0	4	
- SNRIs	0	3	
- no therapy	8	43	
Antipsychotic therapy			ns
- atypical	2	34	
- typical	0	5	
- no therapy	12	92	

[a] The reported onset of cognitive disturbances.
[b] CDR: 1 mild, 2 moderate, 3 severe.
AChE-I: anti-cholinesterase-inhibitors ; SNRI: serotonin-norepinephrine reuptake inhibitors ; SSRI: serotoninreuptake inhibitors.

we report in this population falls within the range reported in studies of mild-to-moderate AD (Amatniek *et al.*, 2006; Lozsadi and Larner, 2006). Published reports describe a wider seizure frequency range in patients with AD (6.8%-26%; Hauser *et al.*, 1986; Amatniek *et al.*, 2006; Lozsadi and Larner, 2006; Romanelli *et al.*, 1990; Förstl *et al.*, 1992; McAreavey *et al.*, 1992; Risse *et al.*, 1990; Randall *et al.*, 1995), possibly owing to differences in the populations examined.

Of the risk factors for seizures in the population, Amatniek *et al.* (2006) identified greater severity as well as duration of symptoms, younger age and less education. When we investigated possible risk factors for seizures in patients with AD, we found no correlation between seizures and education, age or duration of symptoms. An interesting finding, however, was the observation that twice as many AD patients with seizures, relative to those without seizures, had severe dementia, although the difference in the severity of dementia between the two groups failed to reach statistical significance. In a home resident population, Hauser *et al.* (1986) reported an 11% frequency of seizures in subjects in the first 10 years of disease and 26% after 15 years of disease. A community case-control study of severely demented subjects (CDR 3) reported a 23% frequency of seizures; one in four patients with severe dementia developed seizures (Romanelli *et al.*, 1990). In the study of Förstl *et al.* (1992) it was reported that for 11% of patients, motor generalised seizures developed in the advanced stages of disease.

In a study investigating dementia and adult-onset unprovoked seizures in a resident population, Hersdoffer *et al.* (1996) found that the increased risk of epilepsy was not restricted to AD. This finding suggests that any pathological process severe enough to result in cognitive decline may be associated with an increased risk of seizures. The same study reports an eight-fold increase in seizures in non-AD demented patients.

When we investigated other factors that might increase the risk of seizures developing we found that demented males were at increased risk. Although this finding is hard to interpret, especially given the few AD patients with seizures in our study, this gender-related increased risk receives support from other studies reporting a 36% frequency in men and a 64% frequency of seizures in men with advanced AD (Volicer *et al.*, 1995; Risse *et al.*, 1990).

When we analyzed our data to identify the influence of potentially treatable cardiovascular risk factors that favour the onset of seizures, we found that the frequency of seizures was twice as high in patients with hyperlipidaemia compared to those without. The group with seizures contained almost half as many hypertensive patients as the group without seizures, although the difference between the groups failed to reach significance. Notwithstanding, based on the retrospective design of our study and the small study sample, we believe that this is an interesting result and deserves further investigation using studies which should be similarly designed to take into account antihypertensive therapy.

An unexpected finding was that none of the patients in the group with seizures were diabetic. Although this is hard to explain we conjecture that the vascular encephalopathy following a diabetic insult is mainly subcortical and not necessarily related to epileptogenesis.

In our study, there were almost twice as many hyperlipaemic patients in the group with seizures compared to those without. The literature provides no other clinical data, although two Finnish studies indicate that a high cholesterol level in middle age is a risk factor for AD (Sjögren *et al.*, 2006). Several experimental studies demonstrated the role of cholesterol in favouring an abnormal production of aß fragments in beta-amyloid plaques (Höglund and Blennow, 2007). Although we found no published data to support this hypothesis, abnormal deposition of aß fragments in epileptogenic sites, such as the hippocampus and cortical areas (Förstl *et al.*, 1992), might possibly favour seizures.

Hypertension appeared not to influence the risk of seizures. In a previous study, Amatniek *et al.* (2006) showed that treated hypertension may protect against the onset of seizures, whereas Hersdoffer *et al.* (1996) suggested that untreated hypertension may favour seizures in the elderly. Antihypertensive therapy may play a role in the pathogenesis of seizures possibly protecting against cellular degeneration thereby lowering the risk of seizures. Accordingly, recent *in vitro* research has identified a class of antihypertensive drugs that slow deposition of beta-amyloid plaques (Wang *et al.*, 2007).

Our patients' neuroimaging provided no support for an association between radiological abnormalities and seizure onset. Nor was vascular encephalopathy predictive for seizures in AD. Although ischaemic lesions are a well-known risk factor for epilepsy (Silverman *et al.*, 2002), in our study neither lacunar multi-infarct lesions nor leukoaraiosis appeared to be risk factors for the development of seizures. This finding lends further support to the hypothesis that the process underlying seizure onset in AD differs from the process underlying seizure onset in post-stroke epilepsy. A few neuropathological studies on demented patients manifesting seizures indicate the presence of glial changes and neuronal degeneration in specific areas of the brain (hippocampus and neocortex). Hence widespread senile plaque formation in the crucial zones may lead to the development of seizures; neuronal death may affect GABAergic inhibitory circuits and alter the balance between excitation and inhibition, thus favouring seizures (Volicer *et al.*, 1995; Hommet *et al.*, 2008; Förstl *et al.*, 1992).

When we sought to identify the role of antipsychotic and antidepressant drugs in lowering the epileptic threshold, another interesting finding was that although most of our AD patients were taking psychotropic drugs, potentially eliciting seizures, we found no correlation between the intake of these drugs and the onset of seizures, probably because patients were using new generation drugs at low doses. Nor did we find an association between the intake of anti-dementia drugs and seizures.

Because the routine clinical work-up at the time of our study did not include systematic EEG recordings, few patients' records provided EEG data for analysis. Although our study identified frequent interictal EEG abnormalities in patients with seizures, for only a third of these patients the EEG abnormality was of ictal nature. The small number of EEG recordings available prevents us from drawing conclusions as to whether EEG findings have predictive value. Previous studies failed to identify a definite association between seizure onset and EEG abnormalities in AD (Amatniek *et al.*, 2006; Menendez, 2005).

We acknowledge, however, that our study has limitations. Firstly, the study was retrospective in design and the data on seizure onset were collected from outpatients' clinical records not intended for research into epileptic seizures. Secondly, the study was conducted in a population with mild-to-moderate dementia, representing only part of the disease course. The signs and symptoms of seizure attacks are difficult to recognize and infrequently reported, particularly for elderly patients with cognitive impairment. More accuracy and insight on the part of the physician and caregiver may help the recognition and treatment of seizures. History-taking, explicitly designed to elicit epileptic attacks, would presumably identify a larger number of cases and would provide more statistically robust data on the role of clinical and therapeutic risk factors. Seizures play a role in worsening behavioural and cognitive symptoms and hence recognizing and treating patients with seizures is important for the management of dementia. □

Disclosure.
None of the authors has any conflict of interest to disclose.

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