

From here to epilepsy: the risk of seizure in patients with Alzheimer's disease

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ABSTRACT – *Aim.* To describe the association between Alzheimer's disease and seizures by reviewing epidemiological data from available literature and to assess the putative pathophysiological links between neurodegeneration and altered cortical excitability. We also discuss specific antiepileptic treatment strategies in patients with Alzheimer's disease, as well as transient epileptic amnesia as a possible crossroads between degeneration and epilepsy.

Methods. Regarding epidemiology, we searched publications in Pubmed, Medline, Scopus and Web of Science (until September 2015) using the key words "incidence", "prevalence" and "frequency", as well as "Alzheimer's disease" and "seizures". In addition, therapeutic aspects for seizures in Alzheimer's disease were searched using the key words "antiepileptic drugs", "seizure treatment" and "Alzheimer".

Results. The prevalence and incidence rates of seizures were found to be increased 2 to 6-fold in patients with Alzheimer's disease compared to age-adjusted control patients. Treatment strategies have mainly been extrapolated from elderly patients without dementia, except for one single randomised trial, in which levetiracetam, lamotrigine and phenobarbital efficacy and tolerance were investigated in patients with Alzheimer's disease. Mouse models appear to show a major role of amyloid precursor protein and its cleavage products in the generation of cortical hyperexcitability.

Conclusion. A link between Alzheimer's disease and epilepsy has long been described and recent cohort studies have more clearly delineated risk factors associated with the genesis of seizures, such as early onset and possibly severity of dementia. As genetic forms of Alzheimer's disease and experimental mouse models suggest, beta-amyloid may play a prominent role in the propagation of synchronised abnormal discharges, perhaps more via an excitatory mode than a direct neurodegenerative effect.

Key words: Alzheimer's disease, major neurocognitive disorder, seizure, epilepsy

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The continuous aging of the population in the western world leads to an increased occurrence of neurodegenerative diseases and seizures (Cloyd *et al.*, 2006). As

the main cause of dementia (Reitz *et al.*, 2011), Alzheimer's disease (AD) has been studied more extensively, and researchers are realising its complex relationship

with seizures and epilepsy. According to the diagnostic criteria of Dubois *et al.* (2007), probable AD is defined as the presence of a gradual progressive and objective impairment of episodic memory, isolated or in association with other cognitive changes (e.g. visuo-spatial, language, or executive dysfunction), with supportive features such as medial temporal lobe atrophy, abnormal cerebrospinal fluid biomarkers, a specific pattern on PET imaging, or proven autosomal dominant mutation within the immediate family. Definite AD requires either clinical and histopathological evidence, or clinical and causal genetic AD mutation evidence.

It is established that patients with AD have a greater risk of seizures than non-demented patients of similar age. Seizure prevalence of AD patients ranges from 1-22% according to studies (Sjogren, 1952; Hesdorffer *et al.*, 1996; Scarneas *et al.*, 2009) and the incidence rate varies between 4.8 and 11.9/1,000 person-years, which is 2-6-fold higher than subjects of similar age without dementia (Imfeld *et al.*, 2013; Cheng *et al.*, 2015). It is unclear, however, whether seizures are promoted by direct neuronal loss or an excitatory process. Together with cerebrovascular disorders, toxic/metabolic conditions and neoplastic diseases, dementia represents a major cause of seizures in the elderly population. Due to the impact of seizures on cognitive performances in demented patients, it seems crucial to correctly diagnose an epileptic condition in a patient with AD and treat him/her with well-tolerated antiepileptic drugs (AEDs). In this review, we will focus on the epidemiology of seizures and epilepsy exclusively in sporadic and genetic AD patients, and address the pathophysiological mechanisms underlying seizure generation in this population. We will then assess seizure types and EEG abnormalities, and finally discuss treatment strategies.

Methods

Literature search and selection criteria

To address the epidemiological aspects of seizures in patients with AD, we performed a web search on Pubmed, Medline, Scopus and Web of Science, including all studies published until September 2015 using the keywords “incidence”, “prevalence” or “frequency”, associated with “seizures” and “Alzheimer’s disease”. We thus selected retrospective and prospective studies with epidemiological data on seizures in human AD patients. We also looked for references cited in review articles treating this topic. In line with the International League against Epilepsy (ILAE), we used the latest definition of epileptic seizure, *i.e.* sudden and transient signs or symptoms related to an abnormal and excessive discharge of neurons. Accord-

ingly, we considered epilepsy as a chronic medical condition, characterised by an enduring predisposition to epileptic seizures. The current definition requires the occurrence of at least one seizure (Fisher *et al.*, 2014).

In addition, we searched for publications about epilepsy treatment strategies in this particular population, using the key words “antiepileptic drugs”, “seizure treatment” and “Alzheimer”.

Results

Epidemiology of seizures in patients with Alzheimer’s disease

The major aetiologies of seizures in the elderly are cerebrovascular diseases, toxic/metabolic conditions, major neurocognitive disorders, and tumours (Hauser *et al.*, 1996).

Since the 50s, an association between seizures and sporadic forms of AD has been observed. Sjogren *et al.* (1952) noticed a seizure prevalence of 22% in a small sample of pathologically-proven late-stage AD patients. Hauser *et al.* (1986) and Mendez *et al.* (1994) observed a prevalence of 9.6% and 17%, respectively, in larger cohorts of AD patients. The low prevalence rate was probably due to seizure assessment that included only convulsive episodes or was based on historical information and family questionnaires. In a population-based case-control study on first unprovoked seizures, an association with AD was found in 11% of patients (17/145), leading to a six-fold increase compared to patients without dementia (Hesdorffer *et al.*, 1996). Sherzai *et al.* (2014) found a 6.9% AD prevalence among patients hospitalised for seizures in a nationwide US sample, with an odds ratio (OR) of 3.07 (95% CI: 2.98-3.16) compared to the healthy elderly population, which is higher than that for other types of dementias (OR: 2.21; 95%CI: 2.14-2.27). Recent studies have established an incidence rate (IR) of seizures in AD between 4.8 and 11.9/1,000 person-years (Irizarry *et al.*, 2012; Imfeld *et al.*, 2013; Cheng *et al.*, 2015; Cook *et al.*, 2015). Imfeld *et al.* (2013) observed an IR of seizures of 5.6/1,000 person-years in AD patients, while the IR was 0.8/1,000 person-years in non-demented patients. Cheng *et al.* (2015) found an IR of 11.9/1,000 person-years for AD patients and 5.7/1,000 person-years in control subjects. Epidemiological studies on prevalence/incidence of seizures in AD patients are summarised in *table 1*.

The estimation of seizure prevalence is a complex exercise, especially in patients with AD. On one hand, sudden cognitive impairment of demented patients may mislead clinicians to consider a diagnosis of seizure. On the other hand, fluctuations of cognition

can be mistakenly interpreted as a seizure. As AD patients suffer from memory impairment, they might have more difficulties in reporting to their caregiver when experiencing an unusual episode. As we will see later, the majority of seizures in AD patients are focal with secondary impairment of consciousness, which may prove even more difficult to identify than generalised seizures. Moreover, seizures themselves worsen cognition at older age, especially if they are not controlled and remain unrecognised (Noebels, 2011).

There is conflicting evidence about whether AD severity is associated with a higher risk of developing seizures (Romanelli *et al.*, 1990) or that increased risk of seizures is independent of disease stage (Amatniek *et al.*, 2006). In a retrospective record-based study of AD patients followed in a memory clinic in Italy from 2001 to 2006, Bernardi *et al.* (2010) found that 9.7% had at least one unprovoked seizure in a total of 145 patients. Mean duration of the degenerative process was 3.6 ± 1.6 years since the first seizure, and no association was established with severity of dementia. However, in a large cohort study from pooled, prospectively obtained clinical trials with a total of 3,078 patients, a higher risk of seizures with more severe AD was found (Irizarry *et al.*, 2012). Patients with a Mini-Mental State Examination (MMSE) of <18 had a significantly higher seizure hazard ratio (HR) of 3.9 (95% CI: 1.5-10.1) compared to patients with MMSE >18 . Seizure frequency is probably underestimated in retrospective data collection because doctors, caregivers and patients may not recollect the presence of seizures, in particular non-generalised seizures, calling for larger prospective data. The higher risk of being more severely affected is due either to neuroanatomical changes or better surveillance by experienced staff, which likely leads to identification of more possible focal seizures.

In addition, it is unclear whether young age at AD onset for sporadic cases is associated with a higher risk of seizures. Some authors suggested that this might be the case; for example, in the study of Amatniek *et al.* (2006), a prospective follow-up of patients with mild AD with six-month intervals showed a cumulative incidence of unprovoked seizures of nearly 8% at seven years. Younger age at onset of AD (50-59 years) was found to be an independent risk factor, with an 87-fold increase compared to the general population. A younger age at dementia onset has also been considered as a significant predictor (HR: 0.79; 95%CI: 0.70-0.90) of seizures in Cox proportional hazard ratio regression models (Irizarry *et al.*, 2012). In contrast, Mendez *et al.* (1994) found that AD patients with seizures had a younger disease onset, but that epilepsy began at an advanced stage of AD (mean: 6.8 years).

It is established that patients with rare autosomal dominant forms of AD, such as mutation of presenilin-1 (PS1), presenilin-2 (PS2) and amyloid precursor protein (APP), carry a significant risk of seizures (Cabrejo *et al.*, 2006; Larner and Doran, 2006). In a phenotypic study of five families with APP duplication, Cabrejo *et al.* (2006) found that 57% of patients had at least one seizure. Of the PS1 mutations, 20% were reported to be linked to seizures, which may occur either early or late during the course of the disease (Larner, 2011). Determination of seizure types can be difficult and seizures may be mistaken for "confusional episodes".

In patients with Down syndrome, a bimodal distribution of seizures has been observed, first in the first two decades, then in the fifth and sixth decades, usually in association with the onset of dementia (Menéndez, 2005). In this context, up to 84% develop seizures (Lai and Williams, 1989). It appears that a three-phase time course occurs during the second peak, first with onset of dementia, then with progressive epileptic myoclonus, and later with non-epileptic myoclonus. The presence of APOE $\epsilon 3/\epsilon 3$ homozygosity is correlated with this clinical picture (d'Orsi and Specchio, 2014). Cognitive outcome of Down syndrome patients with AD has been retrospectively studied and is considered to be worse whenever associated with seizures (Lott *et al.*, 2012). However, due to the observational design of the studies, it is not clear if seizures lead to a steeper cognitive decline in Down syndrome patients with AD or if epilepsy and dementia are both part of a more severe phenotype of Down syndrome.

Pathophysiology

Since a higher incidence of seizures among patients with AD has been established, it would be useful to understand the reasons for such an elevated susceptibility. Considering that patients with genetic forms of AD (APP, PS1 and PS2) are particularly prone to seizures, a link between amyloid-beta (Ab) and epileptogenicity has been obviously evoked. Mouse model studies may give us more insight into the putative role of Ab on generation of epileptic seizures. Palop *et al.* (2007) showed that accumulation of Ab in the brain could cause epileptiform activity, suggesting a direct excitatory effect of Ab on brain networks rather than a neurodegenerative mechanism. In fact, it is noteworthy to consider that AD mouse models with seizures exhibit little neuronal loss. This finding suggests, at least in experimental studies, that seizures are not related to end-stage degeneration (Chin, 2011). A similar theory is debated in humans - do patients with AD have a higher risk of seizure at the beginning of their neurodegenerative disorder or mainly at the last stage of disease?

Table 1. Studies investigating seizure prevalence/incidence in patients with Alzheimer's disease.

STUDY	STUDY TYPE	Age (years)	Seizure prevalence/incidence	Comment
Sjogren <i>et al.</i> (1952)	Retrospective (autopsy) study of patients with AD	53.0 ± 5.0	22% (4/18)	
Letemendia and Pampiglione (1958)	Retrospective (autopsy) study of patients with AD	31-60	41% (7/17)	
Sulkava (1982)	Cross-sectional study of AD inpatients	-	8% (6/71)	
Hauser <i>et al.</i> (1986)	Retrospective (autopsy) – AD patients	-	9.6% (8/83)	
Heyman <i>et al.</i> (1987)	Prospective – early-onset probable AD	62 (51-74)	14% (13/92)	
Romanelli <i>et al.</i> (1990)	Prospective case-control – mild AD	71.5±4.9	16% (7/44) vs 0/58 controls	
Risse <i>et al.</i> (1990)	Prospective cohort study – hospitalized AD inpatients (with autopsy)	51-83	64% (14/22)	
Forstl <i>et al.</i> (1992)	Prospective (autopsy)	75.4±7.4	11% (6/56)	
McAreavey <i>et al.</i> (1992)	Cross-sectional retrospective – hospitalized patients with dementia	58-94	9.1% (19/208)	
Mendez <i>et al.</i> (1994)	Retrospective (autopsy)	64.1±8.8	17% (77/446)	
Volicer <i>et al.</i> (1995)	Cross-sectional – hospitalized patients with AD	70.6±4.4	36% (27/75)	
Samson <i>et al.</i> (1996)	Cross-sectional population study – patients with probable early-onset AD	36-64	45% (94/198)	
Lozsadi and Larner (2006)	Retrospective study – AD outpatient	49-84	6.8% (12/177)	
Amatniek <i>et al.</i> (2006)	Prospective cohort study – mild probable AD	-	7.7% (12/233)	
Scarmeas <i>et al.</i> (2009)	Prospective cohort study – mild probable AD	74.4±8.9	1.5% (7/453)	
Rao <i>et al.</i> (2009)	Retrospective cross-sectional study – MCI and AD patients	50-100	3.6% (61/1738)	

Table 1. (Continued)

STUDY	STUDY TYPE	Age (years)	Seizure prevalence/incidence	Comment
Bernardi <i>et al.</i> (2010)	Retrospective cross-sectional study – probable AD	51-91	9.7% (14/145)	
Bell <i>et al.</i> (2011)	Retrospective study – AD patients register in Finland	80 (42-101)	2.1%, compared with 1.3% for age-matched controls	
Irizarry <i>et al.</i> (2012)	Cohort study – mild to moderate AD	74.5±9.5	Incidence Rate (IR) 4.8/1'000 person-year (PY)	Independent significant risk factor: younger age, younger age at dementia onset, lower MMSE score, memantine use, antipsychotic use
Vossel <i>et al.</i> (2013)	Retrospective study – AD patients	69.1±9.0 (AD patients with seizures)	3.5% (35/1004)	
Imfeld <i>et al.</i> (2013)	Prospective cohort study – AD, VD and no dementia patients	80.7±6.7 (AD patients) and 82.2±6.6 (VD)	IR 5.6/1'000 PY	IR 7.5/1'000 PY for VD patients
Sherzai <i>et al.</i> (2014)	Retrospective study – incidence of AD vs NAD in patients admitted for seizure	68.2		6.9% AD prevalence among patients hospitalized for seizures – unadjusted OR for AD 3.07 (95% CI, 2.98-3.16) vs 2.21 for NAD (95%CI, 2.14-2.27)
Cook <i>et al.</i> (2015)	Retrospective cohort study – incidence of seizures in AD vs NAD patients	-	IR 8.8/1'000 PY for AD, vs 1.7/1'000 PY for NAD	
Cheng <i>et al.</i> (2015)	Retrospective population-based study – AD vs control patients	75.3±8.2	4.7% (44/937) IR 11.9/1'000 PY for AD, vs 5.7/1'000 PY for control	Significant adjusted predictors: AD (HR = 2.01, 95% CI 1.40–2.90, p < 0.001), age (HR = 1.03, 95% CI 1.00–1.05, p = 0.019)

IR: incidence rate; PY: person-year; HR: hazard ratio; VD: vascular dementia; NAD: non-Alzheimer dementia.

It is suggested that Ab-induced aberrant networks are associated with sprouting of inhibitory neurons in the dentate gyrus of the hippocampus (Palop and Mucke, 2009). In addition, acute exposure to soluble peptides of Ab in hippocampal CA1 cells in mice has been shown to alter intrinsic excitability towards hyperexcitability patterns (Tamagnini *et al.*, 2015). Mice with over-expression of APP also show an increased incidence of seizures and EEG abnormalities, such as sharp wave discharges (Palop *et al.*, 2007; Minkeviciene *et al.*, 2009; Born *et al.*, 2014). *In vitro* experiments with mouse models showed that L-type calcium channel currents (involved in synchronous calcium oscillations) are increased with expression of human APP, independently of Ab production, suggesting a prominent role of APP in neuronal network imbalance (Santos *et al.*, 2009).

Another argument is provided by studies on calbindin, an intracellular protein expressed in granule cells of the dentate gyrus. These cells are excitatory neurons that project information from the entorhinal cortex to mainly the CA3 portion of the hippocampus (Abraham *et al.*, 2009). Calbindin, however, is diffusely expressed in all subfields of the hippocampus and plays a major role in long-term potentiation, plasticity and memory consolidation *via* its calcium binding domains. In normal aging, calbindin expression in cortical areas is globally reduced, while calbindin mRNA remains stable. In contrast, calbindin mRNA decreases in neurodegenerative conditions such as AD, Huntington's disease, Creutzfeldt-Jakob disease (CJD), and fronto-temporal lobe dementia (FTLD) (Iacopino and Christakos, 1990). Stefanits *et al.* (2014) showed a specific loss of calbindin immunoreactivity in dentate granule cells in late stages of AD, as compared to CJD and FTLD.

The particular relationship between Ab and seizures is emphasized by the fact that other dementias, *i.e.* tauopathies and synucleopathies, are generally not associated with a higher risk of seizures compared to the age-adjusted general population. Tau protein may even play a protective role in seizure generation in several mouse models, by preventing long-term potentiation impairment and NMDA receptor dysfunction (Roberson *et al.*, 2011a). However, another model of mutant mice with over-expression of tau protein (fronto-temporal dementia with parkinsonism; FTDP-17) alone has shown increased epileptiform activity (namely spike-waves complexes) and a lower threshold for seizures, suggesting that tau imbalance, as well as Ab, can play a role in epileptogenesis (Garcia-Cabrero *et al.*, 2013). These findings suggest that the concomitant increase in tau and Ab, as is the case in AD, may have a synergistic effect on seizure generation and open the way to treatment against neurodegeneration (Roberson *et al.*, 2011b). Another mechanism of

seizures in AD could be the presence of microbleeds due to cerebral amyloid angiopathy (CAA) since both conditions frequently co-occur (Greenberg *et al.*, 2010; Picco *et al.*, 2011). Indirect evidence for the role of CAA in epilepsy has recently been suggested in a large clinical sample of patients where lobar brain microbleeds were associated with late seizures after an intracerebral haemorrhage (Rossi *et al.*, 2013). Although the coverage of these aspects are beyond the scope of the present manuscript, it is worth considering the role of neuro-inflammation in seizure and neurodegeneration. In rodent models, it has been shown that IL-1 β , IL-6 and TNF are important inflammatory mediators in seizure generation (Bartfai *et al.*, 2007). In addition, exposure to lipopolysaccharides increases intrinsic hippocampal excitability and promotes the expression of a "danger signal" protein called high mobility group box 1 (HMGB1) (Perkins, 2007), which in turn may contribute to cell loss (Ravizza and Vezzani, 2006). Moreover, it is interesting to consider that IL-1 β receptor (IL-1R1) is particularly present in the hippocampus and may modulate seizure threshold. In light of these experimental hypotheses, inflammation may represent the missing link between neurodegeneration and seizures.

Semiology of epileptic seizures and EEG activity

Diagnosing a seizure in a patient with AD can be particularly difficult because sudden episodes of worsened cognition postictally can be interpreted as an ordinary fluctuation of the AD condition. Besides, as the patient has memory impairment, it can prove difficult for him/her to remember an unusual episode, especially in the case of a non-convulsive seizure. In this regard, prospective studies of patients with AD, targeting seizure incidence, should give us more insight into the seizure types and the EEG activity of AD patients. However, these are not yet available.

Vossel *et al.* (2013) studied 54 patients with amnesic mild cognitive impairment (aMCI) or AD in addition to diagnosed epilepsy or with epileptiform activity on EEG. This cohort of patients had transient episodes of cognitive dysfunction and onset of cognitive decline at significantly earlier age (mean age: 64.3 vs 71.1 for patients with aMCI without epilepsy; $p=0.02$). It is of note that the most common type of seizure was focal with impaired consciousness, mostly of a dyscognitive subtype, and that 55% of patients had non-convulsive seizures only. Seizure onset and epilepsy diagnosis preceded or coincided with aMCI or AD diagnosis for 83 and 51% of subjects, respectively. In 31/54 patients, epileptiform activity was described as sharp waves or spikes, and its localization was mostly focal, predominantly in the left temporal lobe. The authors concluded that identifying these patients early and treating them

with AEDs may contribute to an improvement in their clinical course. However, this could not be demonstrated because of the retrospective design and lack of serial neuropsychological testing. Belcastro *et al.* (2007) reported that altered consciousness, transient aphasia and confusion, suggestive of focal seizures, are frequently encountered in AD patients suffering from epilepsy. Nevertheless, in their sample of 233 AD patients initially considered for suspected seizure, a diagnosis of epilepsy was confirmed in 22% of them. Other diagnoses were transient confusional state, syncope, or a metabolic origin. Again, the majority of patients experienced focal seizures with impairment of consciousness, with or without secondary generalization. In a retrospective study including 1,738 patients from the Mayo Alzheimer's disease registry, seizure prevalence was 3.6%, with 72% of patients experiencing focal seizures with impairment of consciousness and 52% generalised tonic-clonic episodes (Rao *et al.*, 2009). The impact of seizures on AD course remains unclear. In an early study on early-onset AD, Samson *et al.* (1996) observed that seizures did not influence disease duration or mortality.

Whereas myoclonic epilepsy is rare in sporadic forms of AD (Rao *et al.*, 2009; Vossel *et al.*, 2013), it has been described in early-onset familial forms of AD, especially in patients with PS-1 mutations (Ezquerria *et al.*, 1999), suggesting an independent phenotype with putative association with dysregulation of calcium homeostasis (Guo *et al.*, 1996). Myoclonic jerks often predate tonic-clonic seizures and are associated with a worse prognosis (Fox *et al.*, 1997).

Generally, it is considered that epileptiform activity, such as spikes and sharp waves, is rather infrequent on surface EEG in patients with dementia. A systematic review of the EEG abnormalities of 1,674 patients in a memory clinic reported such EEG findings in only 3% (Liedorp *et al.*, 2010), while these findings were encountered more often in the cohort studied by Rao *et al.* (2009), in which 38% of patients were reported with epileptiform discharges, mainly uni- or bi-temporal spikes or sharp waves.

Overall, there is a patent lack of studies regarding EEG patterns of seizures in patients with AD and their effect on cognition. In addition, to our knowledge, the direct effect of seizures on memory performance in demented patients has not been studied. However, AD mouse models suggest that repetitive seizures can impair spatial memory performance (Chin *et al.*, 2005).

Transient epileptic amnesia

Transient epileptic amnesia (TEA) is a relatively rare form of temporal lobe epilepsy, characterised by witnessed recurrent episodes of transient memory

impairment, during which other cognitive functions are judged to be intact. Clinical and neurophysiological evidence indicates an epileptic condition, due to the presence of oral automatisms and olfactory hallucinations, epileptiform abnormalities on EEG, and a clear-cut response to AEDs (Butler and Zeman, 2008). In contrast to transient global amnesia, TEA consists of rather short (usually less than one hour) episodes of amnesia, and their repetitive occurrence should prompt clinicians to distinguish this treatable form of TLE from transient global amnesia (Nicastro *et al.*, 2014). In patients with frequent temporal seizures, TEA can also mimic neurodegenerative disorders such as AD. Recent research orientates towards a continuum of TEA and dementia (Rabinowicz *et al.*, 2000). Cretin *et al.* (2012) assessed the possible link between TEA and AD, by studying the case of four patients initially meeting diagnostic criteria for probable or possible TEA, but with persistent memory impairment, despite a well-conducted AED treatment. MRI showed mesial temporal atrophy stage 0 to 3, according to Barkhof's criteria and CSF analysis revealed a decreased Ab42/Tau index.

Aware of the fact that TEA patients present subtle deficits, such as autobiographical memory impairment and long-time forgetting, Butler *et al.*, (2013) examined manual volumetry and automated MRI data of 40 patients with TEA and noticed atrophy in the bilateral hippocampal region, as well as in perirhinal and orbitofrontal cortices. As this particular form of TLE has only been recently described, follow-up studies are currently lacking to understand whether the atrophy is a cause or a consequence of TEA and whether there is an underlying, less severe, degenerative process. TEA has a relatively benign course; seizure control by AEDs is obtained in 88% of TEA subjects (Butler and Zeman, 2008). However, outcome of memory impairment is less clear.

Antiepileptic drugs in patients with Alzheimer's disease

It seems obvious that dementia patients should be treated with AEDs, once an epileptic condition is assessed. However, AD subjects represent a fragile population, as they generally are of advanced age and may suffer more frequently from AED adverse effects, including (additional) drug-induced cognitive impairment or fatigue. Tolerability and efficacy of AEDs in patients with AD have been mainly extrapolated from elderly patients without dementia. In this regard, the following studies are of particular interest. In an international multicentre randomised double-blind controlled study (Saetre *et al.*, 2007), a similar proportion of >65-year-old patients were seizure-free with

Table 2. Studies investigating treatment strategies for seizure management in patients with Alzheimer's disease.

STUDY	Study type	No. of patients	Molecules	Results
Belcastro <i>et al.</i> (2007)	Prospective observational pragmatic study of AD patients with recent onset of seizure (<3 months)	52 with one seizure, 25 with recurrent sz starting treatment	Starting LEV 250 mg bid Daily increment of 250 mg every week until 2000 mg/d	11/25 (44%) sz-free with LEV 500 mg/d +7/25 (total 72%) sz-free with LEV up to 2000 mg/d 4/25 (18%) discontinued LEV because of adverse effects (confusional state, psychomotor agitation) 2/25 : switched to another AED because of recurrent sz 1/25 : lost follow-up
Cumbo and Ligorì (2010)	Prospective randomized three-arm parallel-group study	95, randomly assigned to a monotherapy of LEV, PB or LTG	LEV (n=38) PB (n=28) LTG (n=29) 4-week dose adjustment 12-month dose evaluation period	Response to treatment (<i>resp. Sz-free %, 50-99% response %, total responders %</i>) – <i>follow-up 15-24 months</i> <u>LEV</u> : 28% - 42% - 71% <u>PB</u> : 28% - 35% - 64% <u>LTG</u> : 24% - 34% - 58% Adverse Effects (dizziness, somnolence, headaches, asthenia) <u>LEV</u> : 17%, no withdraw <u>PB</u> : 43%, withdraw 17% <u>LTG</u> : 28%, no withdraw
Rao <i>et al.</i> (2009)	Retrospective open study of AD patients with seizures	39	PHT (38.5%) VPA (17.9%) CBZ (15.4%) GBP (10.3%) PB (2.6%) CLZ (2.6%) 72% (28/39) on monotherapy 28% (11/39) on ≥ 2 AED	Outcome on seizures: 79% modified Engel classification 1 or 2 (sz-free or >95% reduction in sz frequency) 31% (12/39) had AE (e.g. drowsiness)
Vossel <i>et al.</i> (2013)	Retrospective observational study of aMCI and mild AD patients	54	LTG (n=17), dose range 50-600 mg/d LEV (n=16), 250-3000 mg/d PHT (n=6), 100-600 mg/d VPA (n=9), 250-1500 mg/d	Response to treatment (<i>resp. Sz-free %, 50-99% response %, total responders %</i>) <u>LTG</u> : 53% - 41% - 94% <u>LEV</u> : 44% - 50% - 94% <u>PHT</u> : 17% - 33% - 50% <u>VPA</u> : 11% - 66% - 77% Adverse Effects (dizziness, somnolence, headaches, asthenia, ataxia, confusional state) <u>LTG</u> : 28% <u>LEV</u> : 21% <u>PHT</u> : 77% <u>VPA</u> : 18%

AE: adverse effects; AED: antiepileptic drug; aMCI: amnesic mild cognitive impairment; CBZ: carbamazepine; CLZ: clonazepam; GBP: gabapentin; LEV: levetiracetam; LTG: lamotrigine; PB: Phenobarbital; PHT: Phenytoin; Sz: seizure; VPA: valproic acid.

lamotrigine (LTG) and carbamazepine (CBZ) (52% and 57%, respectively; $p=0.45$; OR: 0.8; 95% CI: 0.45-1.43). In a randomised, double-blind trial comparing levetiracetam (LEV), LTG and CBZ, patients aged >60 years old with new-onset epilepsy showed a similar rate of seizure freedom across all three groups, but a highest retention rate for LEV at 58 weeks (61.5%; LTG: 55.6%; CBZ: 45.8%; the difference between LEV and CBZ being significant; $p=0.02$) (Werhahn *et al.*, 2015).

Research of the literature on specific AED treatment strategies in AD patients is scarce. Up to now, only one randomised interventional trial has been reported. Cumbo and Ligorì (2010) led a prospective, randomised, three-arm parallel-group study in patients with seizures and mild-to-moderate AD to determine the efficacy of LEV, LTG and phenobarbital (PB). AEDs were titrated to a dose with weekly increases to the following average dosages: LEV monotherapy was 956 mg (range: 500-2,000 mg/day), PB 90 mg/day (range: 50-100 mg/day), and LTG 57.5 mg/day (range: 25-100 mg/day). Efficacy was determined during a 12-month evaluation phase. While seizure control was similar across the three groups, despite low dosages with LTG, not surprisingly patients with PB suffered from more cognitive side effects. In contrast, patients who received LEV showed better attention and oral fluency performances, but mood was better with prescription of LTG. Tolerability of these three AEDs was assessed and compared with a seizure-free age-adjusted control group. Details of the results are available in *table 2*.

Three other studies addressed drug management of seizures in AD patients, but with an observational design. In their retrospective study including a cohort of 54 patients with mild cognitive impairment (MCI) or AD associated with seizures or EEG epileptiform activity, Vossel *et al.* (2013) studied the clinical response to LEV (daily dose range: 250-3,000 mg), LTG (50-600 mg), valproic acid (VPA: 250-1,500 mg), and phenytoin (PHT: 100-600 mg). The efficacy of LTG and LEV was significantly higher than that of VPA and PHT. With LTG, 53% of patients were seizure-free, while 41% were partial responders. With LEV, the respective outcomes were 44% and 50%, whereas the proportion of seizure-free patients was lower with VPA (11%, but 67% partial responders) and PHT (17% seizure-free patients). However, the daily dose range of VPA can be considered to be lower than that for LTG and LEV. LEV, LTG and VPA were better tolerated compared to PHT ($p<0.05$).

A retrospective open study (Rao *et al.*, 2009) found a 79% rate of good responders (modified Engel classification I or II, i.e. seizure-free or >95% reduction of frequency and fewer than three seizures a year). The most frequently used AEDs were PHT (38.5%), followed by VPA (17.9%), and CBZ (15.4%).

In their prospective observational study of AD patients with seizure onset within <3 months, Belcastro *et al.* (2007) studied the efficacy and tolerability of LEV in 25 patients with advanced AD and recurrent unprovoked seizures. Their data demonstrated that 11/25 (44%) were seizure-free with 500 mg/d, while this proportion increased to 72% (18/25) with increment to 2,000 mg/d. Also, 4/25 (18%) discontinued LEV because of adverse effects (e.g. confusional state or psychomotor agitation), and 2/25 were switched to another AED because of persistent seizures.

Overall, although only few studies have been reported, these suggest that for AD patients who suffer from seizures, newer AEDs have a more favourable side effect profile, but demonstrate a similar efficacy to classic AEDs. However, in some cases, average dosage of some drugs appears very low, and absence of seizures is questionable. Interestingly, Vossel *et al.* (2013) proposed long-term video-EEG and overnight EEGs with sleep EEG to obtain better information on the presence or absence of epileptogenic discharges. Finally, potential pharmacological interference with non-epileptic drugs, such as antihypertensive and anticoagulation drugs, is preferable to avoid life-threatening complications of AED therapy. It is recommended to initiate treatment with low dosage and proceed with a slow titration ("start low, go slow"). In addition, monotherapy should be considered, whenever possible (Arroyo and Kramer, 2001).

Conclusion

Evidence from observational studies suggests that AD (including its sporadic form) is associated with an increased risk of seizures. However, the exact prevalence is difficult to determine due to methodological issues and the difficulty to identify focal seizures with impaired consciousness in dementia patients.

A clear link has been established between epilepsy and AD, affecting particularly early-onset and more advanced AD. However, the pathophysiology of epilepsy is mainly speculative. From a clinical point of view, we need to better identify which AD patients are at risk of developing epilepsy and how to better diagnose seizures using, alongside EEG, additional biomarkers, such as structural MRI or functional neuroimaging. From a molecular standpoint, Ab as well as APP, and perhaps microbleeds secondary to CAA, appear to play a major role. It is of crucial importance to understand the role of APP and its cleavage products in neuronal network imbalance, as this may lead to development of new treatment strategies; in particular in light of the deleterious effects of seizures on pre-existing impaired cognition. In fact, it has been shown that when abnormal activity due to Ab in AD

mouse models is suppressed, cognitive function can be improved (Sanchez et al., 2012; Vossel et al., 2013). Further clinical research is needed in order to evaluate whether neuronal network dysfunction in human patients with AD can be suppressed and cognitive function improved when treated with well-tolerated AEDs. Prospective studies of AD patients with long-term or overnight EEG, as well as cognitive outcome evaluation, are not currently available. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.

None of the authors have any conflict of interest to disclose.

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TEST YOURSELF



- (1) The incidence of seizures in patients with AD is increased by how many fold, compared to age-adjusted general population?
- (2) Which antiepileptic drugs would you recommend in patients with Alzheimer's disease and seizures, in terms of efficacy and tolerance, among valproic acid, lamotrigine and phenytoin?
- (3) Among other hypotheses, it is suggested that seizure generation in patients with Alzheimer's disease is related to sprouting of inhibitory fibers in the hippocampus. Which hippocampal subfield seems to be particularly involved?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".