



Seizures in Alzheimer Disease: Clinical and Epidemiological Data

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Alzheimer disease (AD) and epilepsy are disorders commonly seen in the elderly. Many studies have shown that patients with AD are at increased risk for developing seizures and epilepsy. Whereas, patients with specific types of epilepsy, such as temporal lobe epilepsy (TLE), experience some degree of cognitive dysfunction, questions have been raised as to whether these disorders share some underlying pathophysiologic mechanisms or whether one is an epiphenomenon of the other. In this report, we review some of the available clinical and epidemiologic literature on various aspects of the topic of seizures in AD, including seizure rates and types, risk factors for seizures, electroencephalographic findings, treatment options, limitations, and methodological issues. Overall, multiple aspects of the literature on seizures and epilepsy in AD, including diagnosis, risk factors, the role of EEG in diagnosis, and the response to treatment are not clear and suffer from many methodological limitations and gaps.

Epilepsy and AD are common neurologic disorders for which increasing age is a common and well-established risk factor (1, 2). The potential relation between these two disorders has been supported by experimental and clinical data. From a clinical aspect, patients with AD have an increased risk of developing seizures and epilepsy; thus AD may be an important cause of epilepsy in the elderly. AD and other neurodegenerative conditions represent the presumed etiology for 10% of new onset epilepsy in patients older than 65 (3).

The diagnosis of seizures in patients with AD is not always easy because the manifestation of partial seizures might be hard to recognize and distinguish from other behaviors common in these patients. This may lead to underestimation of the real frequency of seizures in AD. At the same time, the possibility that "funny" or "unusual" behaviors of demented patients are considered seizures, particularly by nonepileptologists, may lead to overestimation of seizure rates.

We briefly review and comment on studies reporting on the risk of seizures in AD, the possible factors modifying this risk, the role of EEG in the diagnosis of epilepsy and its limitations, the efficacy of antiepileptic drugs and the relationship between seizures and interictal epileptiform activity and AD course.

Risk of Seizures in AD

Compared with healthy individuals of the same age, patients with sporadic AD have a 6- to 10-fold increased risk of developing clinical seizures during the course of their illness (4–6). There are many prospective and retrospective studies reporting great variability in the lifetime prevalence of seizures in patients with AD, with rates ranging from 1.5 to 64 percent (5–17). However, it is difficult to accurately assess the real prevalence of seizures in AD because of methodological problems in published epidemiologic and observational studies. The studies in which there is pathologic confirmation of AD have small numbers of subjects, with considerable variability in disease duration and severity. Some prospective and retrospective studies have included other forms of dementia and patients with additional symptomatic causes of epilepsy, such as stroke or hemorrhage. Two recent prospective cohort studies with large numbers of patients with long follow-up and carefully characterized evaluations estimate the overall incidence of seizures in AD at approximately 1 per 200 person-years of observation, suggesting relatively lower frequencies than other studies (17, 18).

There are studies in the elderly reporting recurrence risk after the first seizure as high as 80%, probably because the epilepsy in the elderly population is mainly associated with an underlying structural lesion (15). In AD patients, many of the studies do not distinguish the presence of a single unprovoked seizure from recurrent seizures, namely, epilepsy. To our knowledge, there are no large studies reporting the risk of recurrence of seizures after the first unprovoked seizure in AD, except for few case series that include a small number of



patients (17). In a retrospective autopsy study, 9.6% of patients had an unprovoked seizure after dementia onset, and 6% had epilepsy (5). In terms of the seizure frequency in AD patients, it seems to be quite low, as 71% of the patients experience less than three total seizures (10).

In terms of seizure types, generalized convulsive seizures have been identified in 90% of the cases (10). Other data suggest that 70% of seizures are complex partial seizures (15). Historical information and chart review are often used to determine the diagnosis and type of epilepsy; as a result, it is not clear whether generalized seizures truly represent the majority of seizures in AD or whether, owing to diagnostic bias, partial seizures without convulsive character are being underestimated. Characterization of the clinical manifestations of seizures is usually based on information derived from the patient or the caregiver; there are limitations pertaining to both sources of information. Even in nondemented patients, fewer than 25% (19, 20) are able to report their true seizure frequency for the simple reason that they don't remember the event. In demented patients, this percentage could be even lower. Furthermore, it is difficult for caregivers to report seizure frequency accurately, mainly because they are unaware of how partial seizures manifest. Additionally, it may be challenging to separate seizures from certain behaviors that demented patients often manifest (e.g., fluctuations in alertness and attention, hallucinations, confusion).

Theoretically, seizures in AD should be of focal origin because the neurodegenerative pathology is multifocal. Beyond complex partial seizures, other seizure subtypes such as transient epileptic amnesia (where the patients experience memory problems reminiscent of dementia for repeated short time periods) may also be underestimated (21, 22). Considering all of the above considerations, it remains doubtful whether convulsive seizures represent the majority of seizure types in AD.

In early-onset familial AD (EOFAD), seizures and epilepsy occur more often than in sporadic AD. For example, seizures have been described in 37 to 58 percent of patients with the PSEN1 E280A mutation (23), in 30 percent with presenilin 2 mutations (24), and in 57 percent of patients with amyloid precursor protein (APP) duplications (25). Alzheimer-type neuropathologic abnormalities are demonstrated also in patients with Down syndrome (DS), and DS patients develop dementia at young ages. Up to 84 percent of demented individuals with DS develop seizures (26, 27).

Factors Modifying Risk for Seizures in AD

Seizure prevalence seems to increase with AD duration. Most of the studies support onset of seizures at later stages of the disease (7, 11, 28), on average at 6.8 years after onset (10, 29). This might be because of the increasing accuracy of AD diagnosis, increasing age (but see below for studies refuting this), or increasing severity of the neurodegenerative process. According to the diagnostic criteria for AD (30), seizures in the advanced stage are consistent with a diagnosis of probable AD, while seizures earlier in the course or at onset of dementia suggest uncertain or unlikely diagnosis. There are no reports suggesting increased rates of seizures in mild cognitive impairment (15).

Some studies report that patients with a younger age of AD onset are more susceptible to seizures compared with age-matched populations. Seizure incidence increases 3-fold around the age of 70 and nearly 87-fold around the age of 50 (8, 10, 12, 17, 29). This could be partially explained by higher prevalence of familial AD in younger patients, which has been associated with higher seizure rates, or by a more aggressive AD course in younger AD patients. Nevertheless, this observation contrasts with other studies reporting that neither disease duration nor age of onset were significant risks for seizures in AD patients (5, 6).

AD severity seems to constitute another risk factor for seizures. In prospective studies of patients with probable AD of mild severity, seizures occurred in 1.5 to 16 percent of patients over 1 to 8.5 years of follow-up (11, 12, 17, 31), whereas in studies of institutionalized AD patients, most of whom had more severe dementia, seizure frequencies ranging between 9 and 64 percent were reported (7–9, 13). Dementia severity (12), or worse performance on tests of orientation and information (9), has also been reported to be associated with an increased risk of seizures in AD patients.

African-American ethnicity has been suggested as a risk factor for developing seizures in AD (12). Infrequent, inconsistent reports of other possible risk factors such as diabetes, hypertension, and antipsychotic-cholinesterase inhibitor drugs have also been published (16, 32).

Role of EEG

The prognostic value of scalp EEG in terms of future seizure development in AD patients is unclear. It is well documented that AD patients might have nonepileptiform abnormalities in the EEG, such as θ and δ slowing (33, 34), but very little evidence exists about the presence of epileptiform abnormalities (spikes or sharp waves) and their prognostic value in terms of future seizure development in this patient population. Conceivably, if seizures in AD are related to an underlying hyperexcitability in the hippocampus, we would expect a higher frequency of epileptiform activity in scalp EEG as seen in experimental models and in human mesial temporal lobe epilepsy (22). There are some observational

Key Word Messages

- AD is a risk factor for seizures.
- Seizures clearly occur in AD but are not among the commonest manifestations of the disease.
- Younger age and increasing dementia severity seem to be the most reliable risk factors for seizures in AD.
- The usefulness of the EEG in predicting future seizures in AD has not been adequately investigated.
- When seizures in AD occur, they are typically infrequent, while their control by AEDs is usually fairly easy.
- AED selection is empirically based, mostly on the side effect profile.



studies reporting epileptiform discharges in a minority of AD patients with seizures, but also in some AD patients without seizures. In a study of 1,674 patients with AD and other forms of dementia in a memory disorder clinic, where routine EEGs were performed, epileptiform discharges were detected in only 42 (3%) of the patients—rates very similar to those of the general population (35). The discharges were focal and mainly located in the temporal lobe (35). Sixty percent of these patients did not have clinical seizures at or before the time of EEG, and only 10% of these AD patients, with epileptiform discharges and no clinical seizures at or before the time of EEG, developed seizures later on.

In contrast to the above study, in most reports including AD patients, EEGs are performed in only a subset of patients with AD, limiting our ability to adequately derive safe conclusions. But even if a larger number of AD patients were to be studied with scalp EEG, significant limitations still remain as detection of epileptiform activity is low even in patients with temporal lobe epilepsy (36). The yield would probably increase if video-EEG recordings in epilepsy monitoring units were performed. Nevertheless, practical limitations accompany these studies, particularly in this patient population. Inpatient video-EEG recording studies may be limited by the poor cooperation of AD patients and the confusional episodes associated with hospitalization and changes of environment.

Seizure Treatment in AD

There are no randomized controlled trials exploring the usefulness and efficacy of specific antiepileptic drugs (AEDs) for seizure treatment in AD patients. Some observational studies suggest small differences in the efficacy of AEDs in the elderly (37–40). The efficacy of AEDs in elderly people seems to be either comparable or even better than in younger individuals, with seizure freedom rates as high as 62% (40). Nevertheless, adverse effects of AEDs, either dose-dependent (i.e., dizziness, unsteadiness, lethargy) or specific drug-related (i.e., tremor, hyponatremia, osteopenia) are cause of concern in the elderly, although they seem to be relatively less frequent at lower doses. As a result, it is suggested that decisions on the use of AEDs in AD patients should be based on their pharmacokinetic and side effects profile. Additional suggestions include using an AED with the fewest possible interactions with other medications commonly taken by older patients, and titrating AEDs slowly, employing the lowest possible doses (41). In studies of the general population, the newer AEDs seem to be better tolerated than the first generation AEDs by the elderly (37–40). It also makes intuitive and biological sense to avoid AEDs with deleterious cognitive sequelae such as valproic acid (VPA) and benzodiazepines (BZDs). VPA has been shown to be unhelpful in agitation in AD (42) and is associated with cognitive decline (43). The long term use of BZDs has been associated with an increased risk for cognitive deterioration and falls (44, 45).

Seizures and AD Course

The higher rates of seizures in more advanced dementia could suggest either that seizures lead to higher rates of cognitive decline or those seizures are an epiphenomenon or a marker of more severe dementia stages. Some small series (13) have

reported cognitive deterioration after seizure onset, but these are too limited in terms of sample size and have not taken into account possible AED cognitive side effects. Overall, there is relatively limited literature on the question of the impact of seizures in further AD course and severity.

Conclusions

AD is a clear risk factor for seizures: the risk of seizures and epilepsy in AD seems to increase 3 to 87 times compared with the age-matched general population. The increased risk is age dependent, with higher risk at younger ages. Increasing dementia severity is the other reliable risk factor for seizures in AD. There is variability in reports regarding seizure frequency in patients with AD; the overall incidence of new-onset nonprovoked seizures in AD seems to be approximately 1 per 200 person-years of observation. The role of EEG and its prognostic value in predicting seizures has not been adequately explored. When seizures in AD occur, they seem to be infrequent. In the absence of specific studies, the choice of AEDs of treatment is mostly empirical and based primarily on side effect profiles. The reader is referred to the accompanying article for a review on basic science aspects of epilepsy and Alzheimer's Disease.

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