Seizures and Epileptiform Activity in Early Alzheimer Disease: How Hard Should We Be Looking?

Seizures and Epileptiform Activity in the Early Stages of Alzheimer Disease.


IMPORTANCE: Epileptic activity associated with Alzheimer disease (AD) deserves increased attention because it has a harmful impact on these patients, can easily go unrecognized and untreated, and may reflect pathogenic processes that also contribute to other aspects of the illness. We report key features of AD-related seizures and epileptiform activity that are instructive for clinical practice and highlight similarities between AD and transgenic animal models of the disease. OBJECTIVE: To describe common clinical characteristics and treatment outcomes of patients with amnesic mild cognitive impairment (aMCI) or early AD who also have epilepsy or subclinical epileptiform activity. DESIGN Retrospective observational study from 2007 to 2012. SETTING: Memory and Aging Center, University of California, San Francisco. PATIENTS: We studied 54 patients with a diagnosis of aMCI plus epilepsy (n = 12), AD plus epilepsy (n = 35), and AD plus subclinical epileptiform activity (n = 7). MAIN OUTCOMES AND MEASURES: Clinical and demographic data, electroencephalogram (EEG) readings, and treatment responses to antiepileptic medications. RESULTS: Patients with aMCI who had epilepsy presented with symptoms of cognitive decline 6.8 years earlier than patients with aMCI who did not have epilepsy (64.3 vs 71.1 years; P = .02). Patients with AD who had epilepsy presented with cognitive decline 5.5 years earlier than patients with AD who did not have epilepsy (64.8 vs 70.3 years; P = .001). Patients with AD who had subclinical epileptiform activity also had an early onset of cognitive decline (58.9 years). The timing of seizure onset in patients with aMCI and AD was nonuniform (P < .001), clustering near the onset of cognitive decline. Epilepsies were most often complex partial seizures (47%) and more than half were nonconvulsive (55%). Serial or extended EEG monitoring appeared to be more effective than routine EEG at detecting interictal and subclinical epileptiform activity. Epileptic foci were predominantly unilateral and temporal. Of the most commonly prescribed antiepileptics, treatment outcomes appeared to be better for lamotrigine and levetiracetam than for phenytoin. CONCLUSIONS AND RELEVANCE: Common clinical features of patients with aMCI- or AD-associated epilepsy at our center included early age at onset of cognitive decline, early incidence of seizures in the disease course, unilateral temporal epileptic foci detected by serial/extended EEG, transient cognitive dysfunction, and good seizure control and tolerability with lamotrigine and levetiracetam. Careful identification and treatment of epilepsy in such patients may improve their clinical course.

Commentary

My standard epilepsy talk for medical students used to include the following: The incidence of epilepsy has a bimodal distribution, and the causes of epilepsy in children are different from those in older adults. New-onset epilepsy in the elderly is often a consequence of accumulated injuries to the brain, including from stroke, brain tumors, and neurodegenerative diseases. Although I did not explicitly say that epilepsy was an end-stage feature of Alzheimer disease (AD)—the result of advanced neuronal and synaptic loss—I implied that this was the case and made that implicit assumption myself. Clearly, this thinking needed revision.

There is now substantial and growing literature addressing the interface between Alzheimer disease and epilepsy. Epidemiological studies clearly indicate that Alzheimer disease confers an increased risk of seizures and epilepsy: The incidence rate is increased about sevenfold in patients with AD compared to non-demented controls (1). A number of potential risk factors for developing seizures in AD have been identified, including antipsychotic drug use, African-American race, epileptiform findings on EEG, and greater cognitive impairment at baseline (2, 3). However, the most robust association has been with young age at dementia onset (4). While seizures can appear at any stage of the disease, the odds of developing epilepsy in AD are highest in young patients with AD and early in the disease course.

Those with genetic causes of AD, who also have earlier onset of disease, appear to be at especially high risk of developing comorbid epilepsy. Patients with the most common
Seizures in Alzheimer Disease

cause of autosomal dominant AD—mutation in the preseni- lin-1 gene on chromosome 14—have about a 1 in 5 chance of developing seizures. In Down syndrome (DS), which shares many neuropathological features with AD, up to 84% of indi- viduals with DS and dementia develop seizures (5). Animal models of AD—including transgenic animals that express human amyloid precursor protein, and have elevated levels of Aβ—have shown a high incidence of seizures in early stages of disease, before evidence of neuronal loss (6). In this model, continuous EEG monitoring was required to detect seizures, and most were nonconvulsive (6). This early and frequent appearance of seizures has led several investigators to hypothe- size that excitatory circuits and seizures may not simply be a consequence of an advancing neurodegenerative process but instead may be intimately connected with the pathogen- esis of AD and may drive a positive feedback loop that results in cognitive decline (7).

In this context, Vossel and colleagues sought to better describe epilepsy in early AD and its precursor, amnestic mild cognitive impairment (aMCI). From a single tertiary care memory clinic, they retrospectively identified cases of aMCI or probable AD with comorbid clinical diagnosis of epilepsy or evidence of subclinical epileptiform activity on EEG. From this group, they excluded those with early-in-life or alternative causes of seizures, yielding 12 aMCI and 35 AD patients with epilepsy and 7 AD patients with subclinical epileptiform activity on EEG. This subgroup was compared to their larger clinic population without epilepsy. They retrospectively established dates for the onset of cognitive symptoms, seizures, and diag- noses of aMCI/AD and epilepsy. They also analyzed available MMSE scores, EEG reports, and outcomes of antiepileptic drug (AED) trials.

In the aMCI and AD patients, cognitive decline began 5 to 7 years earlier in those with epilepsy than in those without. On- set of cognitive problems before age 65 was twice as frequent in the epilepsy + AD and epilepsy + aMCI groups compared with the non-epilepsy cohort, in spite of the fact that the epilepsy group had more years of education at baseline. Epi- lepsy onset was clustered near the onset of cognitive decline; seizures preceded or coincided with a diagnosis of aMCI or AD in 83%, and a formal epilepsy diagnosis was made prior to or at the same time as the aMCI or AD diagnosis in 51%, mirroring previous reports in humans and in animal models of AD.

The most common seizure type in this population was complex partial seizures with dyscognitive symptoms, and more than half of the cohort had only nonconvulsive seizures. These findings are consistent with prior studies suggesting that seizures in AD can be subtle and difficult to distinguish from dementia-related fluctuations in attention and cognition. In the subset of 39 patients evaluated with EEG, 62% had epileptiform findings on EEG, nearly all focal, and most commonly unilateral in the temporal or frontotemporal region.

Seizures were treated most often with lamotrigine (n = 25) or levetiracetam (n = 23), though a smaller number were treated with phenytoin (n = 9) or valproate (n = 11). With lamotrigine or levetiracetam, about half of the patients became seizure free, and the majority of the others were deemed partial responders (lamotrigine 53% seizure free, 41% partial responders; levetiracetam 44% seizure free, 50% partial responders). Phenytoin was significantly more poorly tolerated and less efficacious (17% seizure free, 33% partial responders). Valproate showed intermediate responses (11% seizure free, 67% partial responders). Previous studies in the AD/epilepsy population have also identified differences in tolerability, with levetiracetam better tolerated than an older AED (phenobar- bital), and lamotrigine showing positive mood benefits (8).

Early excitement about valproate conferring neuroprotective benefits was tempered by later reports suggesting that valproate use led to accelerated brain atrophy and cognitive decline (9, 10).

In isolation, the study by Vossel and coworkers has limitations. The generalizability of the findings of this study is uncertain; not only was the study population drawn from a single tertiary care center but from one that specializes in early-onset cases and that attracts a highly educated cohort. The study also carries many of the limitations inherent in a retrospective observational study: Clinic notes may have been incomplete, assessments were not pre-specified, and caregivers may have had recall bias in determining onset of cognitive symptoms, among others.

However, in context, the report from Vossel et al. builds on existing knowledge about the relationship between epilepsy and AD. It emphasizes that epileptic activity may be more prevalent in early AD than previously recognized. It extends clinical observations to aMCI, at the leading edge of AD. It provides some guidance and raises more questions about how we should assess and treat patients with AD and epilepsy.

There is much that we still don’t know. Basic scientists working to define a pathogenic role of epileptiform activity and seizures in AD may identify new avenues for treatment. Clinical researchers may better define the method and intensity of monitoring required to detect subtle seizure activity. Clinicians must maintain a high degree of suspicion for subtle seizures in patients with AD—including in aMCI and early AD—and investigate with available diagnostic tools. Routine EEG may be insufficiently sensitive, and even extended EEG studies may not adequately sample from hippocampal sources and may underestimate the prevalence of epileptiform activity. When needed, treatment should be preferentially with newer generation AEDs.

So, what should I tell our medical students about epilepsy in AD? It is complicated. Seizures and epilepsy may commonly appear early in the course of the AD and contribute to cognitive dysfunction. Hyperexcitability, epileptiform activity, and subtle seizures may be directly involved in the disease pathogenesis. And I expect I will be revising my lecture again in a few years.

by David Spencer, MD

References


Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

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   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

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   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

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5. Journal Issue you are submitting for: 14-1, 14-2, 14-3

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