

HOW IMPORTANT IS ALZHEIMER'S DISEASE AS A RISK FACTOR FOR UNPROVOKED SEIZURES AND EPILEPSY IN THE ELDERLY?

Seizures in Alzheimer Disease: Who, When, and How Common? Scarmeas N, Honig LS, Choi H, Cantero J, Brandt J, Blacker D, Albert M, Amatniek JC, Marder K, Bell K, Hauser WA, Stern Y. *Arch Neurol* 2009;66:992–997. **BACKGROUND:** Transient symptoms in Alzheimer disease (AD) are frequent and include seizures, syncope, and episodes of inattention or confusion. The incidence of seizures in AD and predictors of which patients with AD might be more predisposed to them is based primarily on retrospective studies and is not well established. **OBJECTIVE:** To determine the incidence and predictors of new-onset unprovoked seizures. **DESIGN:** Prospective cohort study. **SETTING:** Three academic centers. **PATIENTS:** Four hundred fifty-three patients with probable AD observed prospectively from mild disease stages since 1992. **MAIN OUTCOME MEASURE:** Informant interviews every 6 months included questions about whether the patient had a seizure (convulsion, fainting, or “funny” spell) and whether diagnosis or treatment for epilepsy or seizure was made. Two epileptologists independently retrospectively reviewed all available medical records for 52 patients with positive responses to either of these questions, and using a specific checklist form, events were diagnosed as to whether they were unprovoked seizures (intrarater concordance, $\kappa = 0.67$). Diagnosis of unprovoked seizures constituted the event in survival analyses. Potential predictors included sex, age, race/ethnicity, educational achievement, duration of illness, baseline cognition and function, depression, medical comorbidities, and time-dependent use of cholinesterase inhibitors and neuroleptic agents, apolipoprotein E genotype, and previous electroencephalographic findings. **RESULTS:** Over the course of 3,518 visit-assessments (per patient: mean, 7.8; maximum, 27), 7 patients (1.5%) developed seizures. Younger age was associated with higher risk (hazard ratio, 1.23; 95% confidence interval, 1.08–1.41; $P = .003$ for each additional year of age) of seizure incidence. No other predictor was significant. The overall incidence of seizures was low (418 per 100 000 person-years of observation) although significantly higher than expected for idiopathic unprovoked seizures in similar age ranges of the general population (hazard ratio, 8.06; 95% confidence interval, 3.23–16.61). **CONCLUSIONS:** Unprovoked seizures are uncommon in AD, but they do occur more frequently than in the general population. Younger age is a risk factor for seizures in AD.

COMMENTARY

The incidence of epilepsy increases progressively in old age, with the highest incidence rates recorded after age 75 years (1). New onset epilepsy in the elderly is usually symptomatic, even though a considerable proportion of patients have no identified etiology. In one study, the most commonly recognized etiology was cerebrovascular disease, accounting for about one-third of patients older than 64 years, while degenerative disease accounted for 11.5% of patients (1). Alzheimer's disease, the most common degenerative disease of the CNS and the most common cause of dementia, is a recognized risk factor for epilepsy. For example, 8 of 81 patients with autopsy-confirmed disease developed unprovoked seizures after the onset of dementia, reflecting an incidence that is 10 times higher than expected (2). Subsequent studies showed even higher proportion of affected patients: in one study, 7 of 44 patients (16%) with Alzheimer's disease developed generalized tonic-clonic seizures as compared to none of 58 healthy controls (3). Three of these patients had autopsies that failed to identify any neuropathologic epileptogenic factors, other than Alzheimer's disease. In another study, 77 (17%) of 446 patients

with autopsy-confirmed Alzheimer's disease developed unprovoked seizures (4). The patients with seizures had a younger age of dementia onset than patients who did not develop seizures, but seizures were usually a late feature, seen with advanced disease, on average at 6.8 years after onset. An even higher incidence of seizures (21%) was reported among institutionalized patients with Alzheimer's disease (5). The clinical association between seizures and Alzheimer's disease is supported by experimental evidence. For instance, high levels of β -amyloid, the main constituent of Alzheimer plaques, caused epileptiform activity in a mouse model (6). In addition, presence of the apolipoprotein E- $\epsilon 4$ allele, a major genetic risk factor for Alzheimer's disease, is also associated with increased risk of late post-traumatic seizures (7).

In the current study, Scarmeas et al. also concluded that Alzheimer's disease was a risk factor for unprovoked seizures and that younger age was a predictor, however they found a much lower incidence than previously reported. The reason for the discrepancy between this and other published studies may be that patients were enrolled in the early stages of the disease in the Scarmeas et al. trial. Another important differentiating factor may be the rigorous criteria used for the diagnosis of seizures: two epileptologists had to reach an agreement on the diagnosis, after considering the available data. While only seven patients were eventually considered to have had unprovoked seizures, 45 others gave at least one positive response to

the seizure-related questions used in the study. Only nine events were considered nonepileptic, based on adequate data. The remaining 36 events could not be classified because of insufficient information. When these 36 events were included as seizures, the estimated risk of unprovoked seizures with Alzheimer's disease increased to 13%, at 5 years from inclusion in the study.

It is likely that the current study and other studies may have missed seizures that lacked a prominent motor component, such as complex partial seizures manifesting mostly with altered awareness and responsiveness. Even though one recent study suggested that complex partial seizures may be the most common seizure type in dementia (8), six of the seven (86%) seizures reported in the current study were convulsive; and in another study, 69 of 77 (90%) of patients had generalized tonic-clonic seizures (4). Patients with Alzheimer's disease may not be able to report subjective experiences associated with complex partial seizures, and observers may find it difficult to distinguish confusion and altered responsiveness that is due to seizures from similar manifestation that result from fluctuations in dementia.

Seizures associated with Alzheimer's disease appear to be infrequent. The current study reported that four patients had only a single seizure. Another study reported 71% of affected patients had less than three seizures each (4). Such data raise the question of whether these single seizures have to be treated. However, as discussed, mild complex partial seizures may not be recognized in this patient population; thus, it is quite possible that the recurrence rate is underestimated. The recurrence rate after a single, unprovoked seizure is estimated as high as 80% in the elderly (9), and antiepileptic drug (AED) therapy is therefore recommended after a single seizure in this age group. In the current study, five of the seven patients with seizures were treated with an AED. Epilepsy in the elderly is generally responsive to AED therapy at low doses (9). In one recent series, 79% of patients with recurrent seizures and Alzheimer's dementia were reported to have an excellent response to AED therapy (8). Using a single nonenzyme-inducing AED, at a low dose, may help avoid interactions and adverse experiences among these patients, who are likely to be receiving other medications as well. If seizures fail to come under control, it is important to consider the potentially proconvulsant effect of acetylcholinesterase inhibitors, which frequently are used for the treatment of dementia. The current study did not find the use of these agents to be a predictor of unprovoked seizures. However, other investigators have provided evidence that they may exacerbate seizures in patients with epilepsy (10).

The relationship between dementia and epilepsy is not exclusively one directional, with the dementing illness possibly causing epilepsy, as importantly, new onset epilepsy in the elderly may present with cognitive decline and may be misdi-

agnosed as a progressive dementia (11,12). In such instances, cognitive function improves and stabilizes with successful therapy, making it unlikely that seizures are an initial presentation of Alzheimer's disease. In addition, dementia can be a result of adverse cognitive effects from AEDs; for instance, valproate therapy among elderly patients has been associated with a reversible syndrome of cognitive impairment and Parkinsonism (13). It is possible that patients with epilepsy or AED-induced cognitive impairment may inflate the apparent incidence of epilepsy in the setting of dementia. The determination that seizures are secondary to Alzheimer's disease can be made with most confidence when seizures appear as a late feature, after years of progressive dementia. When seizures and dementia start at around the same time, there is an increased likelihood that the dementia may be a consequence of epilepsy or its therapy rather than of true Alzheimer's disease.

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References

1. Hauser WA. Seizure disorders: the changes with age. *Epilepsia* 1992;33(Suppl 4):S6-14.
2. Hauser WA, Morris ML, Heston LL, Anderson VE. Seizures and myoclonus in patients with Alzheimer's disease. *Neurology* 1986;36:1226-1230.
3. Romanelli MF, Morris JC, Ashkin K, Coben LA. Advanced Alzheimer's disease is a risk factor for late-onset seizures. *Arch Neurol* 1990;47:847-850.
4. Mendez MF, Catanzaro P, Doss RC, Arguello R, Frey WH, 2nd. Seizures in Alzheimer's disease: clinicopathologic study. *J Geriatr Psychiatry Neurol* 1994;7:230-233.
5. Volicer L, Smith S, Volicer BJ. Effect of seizures on progression of dementia of the Alzheimer type. *Dementia* 1995;6:258-263.
6. Palop JJ, Mucke L. Epilepsy and cognitive impairments in Alzheimer disease. *Arch Neurol* 2009;66:435-440.
7. Diaz-Arrastia R, Gong Y, Fair S, Scott KD, Garcia MC, Carlile MC, Agostini MA, Van Ness PC. Increased risk of late posttraumatic seizures associated with inheritance of APOE epsilon4 allele. *Arch Neurol* 2003;60:818-822.
8. Rao SC, Dove G, Cascino GD, Petersen RC. Recurrent seizures in patients with dementia: frequency, seizure types, and treatment outcome. *Epilepsy Behav* 2009;14:118-120.
9. Ramsay RE, Rowan AJ, Pryor FM. Special considerations in treating the elderly patient with epilepsy. *Neurology* 2004;62:S24-29.
10. Fisher RS, Bortz JJ, Blum DE, Duncan B, Burke H. A Pilot Study of Donepezil for Memory Problems in Epilepsy. *Epilepsy Behav* 2001;2:330-334.
11. Hogg P, Smith SJ, Scahill RI, Chan D, Harvey RJ, Fox NC, Rossor MN. Epilepsy presenting as AD: neuroimaging, electroclinical features, and response to treatment. *Neurology* 2002;58:298-301.
12. Ito M, Echizenya N, Nemoto D, Kase M. A Case Series of Epilepsy-derived Memory Impairment Resembling Alzheimer Disease. *Alzheimer Dis Assoc Disord* 2009.
13. Armon C, Shin C, Miller P, Carwile S, Brown E, Edinger JD, Paul RG. Reversible parkinsonism and cognitive impairment with chronic valproate use. *Neurology* 1996;47:626-635.