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Incidence and Predictors of Seizures in Patients with Alzheimer's Disease

*‡Joan C. Amatniek, *‡W. Allen Hauser, ‡Carrie DelCastillo-Castaneda, *‡Diane M. Jacobs, *‡Karen Marder, *‡Karen Bell, ‖Marilyn Albert, §Joseph Brandt, and *†Yaakov Stern

*Departments of *Neurology and †Psychiatry and ‡the Gertrude H. Sergievsky Center, Columbia University College of Physicians and Surgeons, New York, New York; §Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland; and ‖Departments of Psychiatry and Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.*

Summary: *Purpose:* To determine cumulative incidence and predictors of new-onset seizures in mild Alzheimer's disease (AD) with a cohort followed prospectively. Limited information is available on the incidence of seizures, and no reports exist of seizure predictors in AD patients.

Methods: Mild AD patients were prospectively followed at 6-month intervals to estimate incidence of unprovoked seizures, compare age-specific risk of unprovoked seizures with population norms, and identify characteristics at baseline (demographics, duration and severity of AD, physical and diagnostic test findings, and comorbid medical and psychiatric conditions) influencing unprovoked seizure risk. Review of study charts and medical records supplemented coded end-point data.

Results: The cumulative incidence of unprovoked seizures at 7 years was nearly 8%. In all age groups, risk was increased compared with a standard population, with an 87-fold increase in the youngest group (age 50–59 years) and more than a threefold increase in the oldest group (age 85+ years). In multivariate modeling, independent predictors of unprovoked seizures were younger age [relative risk (RR), 0.89 per year increase in age; 95% confidence interval (CI), 0.82–0.97], African-American ethnic background (RR, 7.35; 95% CI, 1.42–37.98), more-severe dementia (RR, 4.15; 95% CI, 1.06–16.27), and focal epileptiform findings on electroencephalogram (EEG) (RR, 73.36; 95% CI, 1.75–3075.25).

Conclusions: Seizure incidence is increased in people starting with mild-to-moderate AD. Younger individuals, African Americans, and those with more-severe disease or focal epileptiform findings on EEG were more likely to have unprovoked seizures. **Key Words:** Alzheimer's disease—Seizures—Cumulative incidence—Predictors—Prospective cohort.

Two prospective studies have noted a significantly higher incidence of seizures in Alzheimer's disease (AD) patients than in nondemented elderly controls (1,2), and AD was a significant risk factor for seizures in one prior case–control study (3). These studies did not thoroughly explore the clinical features that might be predictive of later seizures. Two studies reported no association between seizures in AD and age at AD onset (2), prior EEG findings (2), or apolipoprotein E (ApoE) status (4).

In this study, we examined the age-specific incidence of a first unprovoked seizure in AD patients relative to others of the same age. We also identified characteristics early in AD that are predictive of future unprovoked seizures. We used data from the Predictors study, which has been collecting data semiannually for nearly 10 years on patients with mild AD at study entry, many of whom had been recently diagnosed (5). This study's prospective design and regular data collection permitted calculation of the cumulative incidence of unprovoked seizures and appraisal of baseline characteristics of the cohort as predictors of unprovoked seizures.

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Address correspondence and reprint requests to Dr. Y. Stern at Sergievsky Center, 630 W. 168th Street, New York, NY 10032, U.S.A. E-mail: ys11@columbia.edu

METHODS

Study design

Starting in 1989, 236 subjects were recruited consecutively, except for those unwilling to provide informed consent or living too far from the centers to be seen regularly in follow-up, from patients seen by Columbia University's Neurology Department, Johns Hopkins University's Psychiatry Department, and Massachusetts General Hospital's Geriatric Neurobehavioral Center, including patients who lived at home or in long-term care facilities. These patients were seen by private physicians or clinic staffs and were or were not enrolled in clinical trials. All patients met diagnostic criteria for probable AD

based on National Institute of Neurological Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS-ADRA) criteria (6). Inclusion criteria were Modified Mini Mental Status (7) score of ≥30 (16 on the standard Mini Mental State Examination); no antipsychotic medication use for ≥1 month; no abnormality of head magnetic resonance imaging (MRI) or computed tomography (CT) scan except for atrophy or small, silent subcortical lesions; demonstrated willingness to return for follow-up; and ability to speak English and to retain an English-speaking advocate. Exclusion criteria included alcohol or drug dependency at time of study entry, CNS infection or non-AD causes of dementia, clinical or historic evidence of cortical stroke, history of schizophrenia or schizoaffective disorder before the onset of intellectual decline, or any electroconvulsive treatment sessions during the prior 2 years or ≥10 treatment sessions during the patient's lifetime. History of seizures was not an exclusion criterion for enrollment in the Predictors Study, but it was for this analysis.

Data collected at baseline included medical history, demographic information, and a head image, either a CT scan or MRI. Data collected both at baseline and every 6 months included neurologic, neuropsychologic, psychiatric, medical, functional, and living status (5). An EEG was not required but was obtained in nearly 60% of the patients as part of the routine dementia workup before or at the baseline visit. EEGs, which were acceptable quality to the patients' clinicians at these three tertiary care institutions, were not reanalyzed, but laboratory reports were coded for the analysis based on specific criteria for slow dominant rhythm, focal slowing, intermittent rhythmic slowing, other slowing, focal epileptiform activity, and generalized epileptiform activity. Race was self-defined, and hypertension was determined in a medical interview.

Seizure end point

The questions in the original database addressing the occurrence of a seizure were as follows: "In the past 6 months, has the patient been diagnosed or treated for epilepsy or seizures?" and "Has the patient had a seizure (fit, faint, or funny spell) since the last visit?" Because the second question could also be interpreted as asking about syncope or pseudoseizures, an affirmative response was considered as a possible not probable seizure. To increase the likelihood of an event's being an unprovoked seizure, additional information was culled by reviewing the original questionnaires and medical records of subjects with an affirmative answer to either of the two questions in any interval, including baseline, for noncoded information. After review of all identified charts, each possible seizure was evaluated for seizure likelihood by two neurologists. A probable seizure required either an affirmative response to the first question, or an affirmative response to the second question and a circle around seizure or an inserted description of the event consistent with unprovoked seizure. Chart information was used to clarify research data. A detailed description of the event was always considered the most accurate information. Each neurologist independently evaluated the study charts and medical records from the date of the event, reaching consensus if the two opinions varied on seizure likelihood. These were conservative determinations. If doubt existed, an event was not classified as a probable seizure.

Incidence

After exclusion of prevalent cases, a Kaplan–Meier survival curve was computed to estimate cumulative incidence of unprovoked seizures. Data were entered at 6-month intervals for events occurring in the previous period. Cases were entered at study recruitment. Seizures were considered an end point. Subjects were withdrawn at death (seizure free) or at the date of last follow-up. We did not have a non-AD control group. Age-specific incidence in 10-year age groups was calculated and compared with age-specific incidence in a referent cohort (8), resulting in incidence ratios.

Predictors

Choice of possible predictors of seizures in patients with AD was based on clinical, laboratory animal, and epidemiologic knowledge of seizures and prior experience with the variables in this study. The potential predictors evaluated are listed in Table 1.

Each variable was screened by calculating mean t tests or χ^2 tests comparing patients who had seizures with those who did not and their corresponding p values or risk ratios. For variables that showed promise, by strength of association or by significance, a univariate Cox Proportional Hazards regression was performed to determine beta, risk ratio, and 95% confidence interval. We defined a strong risk ratio as >1.05 or <0.95 per unit increment for continuous and >2.00 or <0.50 for categoric variables; and a promising p value as <0.20. Potential interaction was explored by constructing and testing interaction terms between two predictor variables. Possible confounding was evaluated by comparing the univariate estimate for each variable that passed screening criteria with the beta from a bivariate model with age, and vice versa. Confounding was considered present if the estimate had changed ≥10%. Multivariate regressions were performed on variables with promising significance or that were strong in the univariate analysis. Multivariate regressions were completed with and without EEG findings because EEGs were available for only 136 of the 233 cases, or 58.37%. If a variable was not included in the model without EEGs, it was not tested in the model with EEGs.

TABLE 1. *Variables studied as possible predictors*

Demographic characteristics Education, gender, race, age at study intake
Disease duration Neurologist's estimation of duration of illness at recruitment
Severity Modified Mini Mental Status Examination
Physical examination Presence of any positive finding on neurologic examination except for mental-status changes consistent with a diagnosis of dementia such as memory loss
Diagnostic tests EEG-focal epileptiform findings,[a] slow dominant rhythm,[b] head images, and ApoE-4 status
Factors associated with seizures in general populations[c] Congestive heart failure, head trauma with loss of consciousness, hypertension, autoimmune disorders, systematic malignancies, thyroid disease, drug abuse, alcohol use, depression, use of antidepressant medications

[a]Criteria for focal epileptiform activity were mention in the narrative report: "cases with focal spikes, multifocal spikes of bilateral independent spikes."

[b]Criteria for slow dominant rhythm were mention of in the narrative report: ". . . .8 Hz. or less. . . . Thus, any record with a background frequency of 8 Hz. or less should be considered abnormal in this respect. However, if a range is mentioned with an upper level >8 Hz. (e.g., 7–8.5 Hz), then this category is considered normal. If recording during the awake state was inadequate to allow a statement as to dominant rhythm, then code as unknown. Low-voltage, fast dominant rhythms are considered normal."

[c]Because data were not available for family history of seizures and use of specific antihypertensive medications were not in the data base, these variables were not studied. Stroke was not investigated as a variable because it was an exclusion criterion for the study, but small lacunae were investigated in supplemental analyses. Additionally, chronic renal disease was not studied because of its absence at baseline in the cohort.

RESULTS

Incidence

Three subjects reported a history of seizures at the initial visit and were therefore excluded from the analysis. Of the remaining 233 subjects with probable AD who were followed up from zero to 8.95 years (median follow-up period of 5.99 years), in 12, seizures developed, all of which were unprovoked. No patients were identified with acute symptomatic seizures. The initial first seizure occurred at 1 year after enrollment. The last incident seizure in this series occurred at 6.55 years of follow-up. The median time to first seizure was 4.06 years. The cumulative incidence of seizures was estimated to be 7.75% by 7 years of follow-up (Fig. 1).

Unprovoked seizure incidence in the total group was 0.87% (12 incident seizures/1,374 person-years observed). Unprovoked seizure incidences in 10-year age intervals were 4.26% (two of 47) for ages 50–59 years, 1.55% (four of 258) for ages 60–69 years, 0.57% (three of 527) for ages 70–79 years, and 0.55% (three of 542) for ages 80+ years. This incidence was higher than expected in the general population (8). The increase was greatest for the youngest group of 50 to 59 (IR, 86.66; 95% CI, 20.66–363.50; $p < 0.001$) and least for the oldest group of 80+ (IR, 3.19; 95% CI, 0.95–10.66; $p = 0.08$) (Fig. 2).

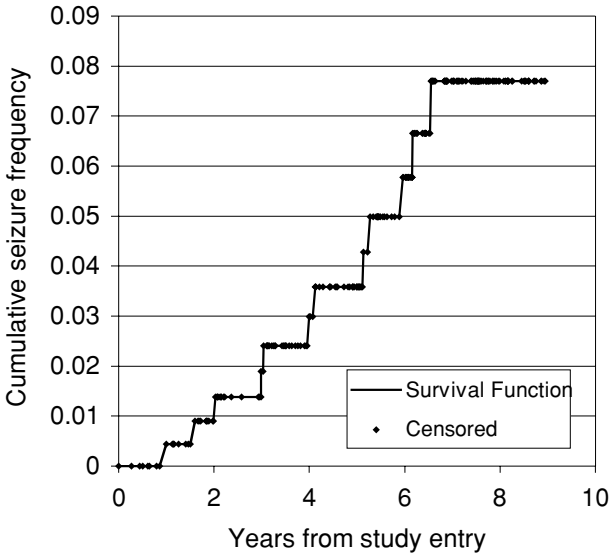

FIG. 1. Cumulative incidence of seizures in Alzheimer disease: in all races.

Predictors of unprovoked seizures

In univariate regressions, presented in Table 2, younger age was predictive (RR, 0.92 continuous; 95% CI, 0.82–0.97; $p = 0.01$). In addition, we used the univariate analyses to screen for inclusion in the multivariate analyses, according to the criteria set forth in the Methods section. In these regressions, African-American ethnic background, greater severity (based on MMSE score) at initial visit, longer duration of symptoms, less education, and focal epileptiform findings were also predictive of seizures,

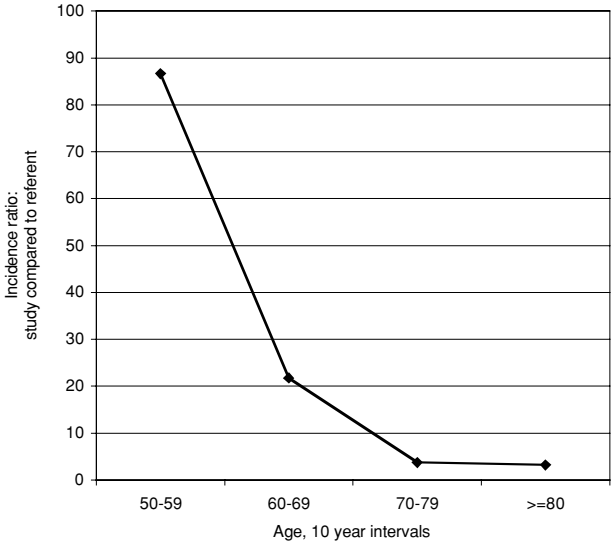

FIG. 2. Incidence ratio by age: observed compared with expected, in all races.

TABLE 2. *Cox regression models of seizure predictors in AD: all races*

	Univariate	Multivariate without EEG variables	Multivariate with EEG variables
Variable	RR (95% CI)	RR (95% CI)	RR (95% CI)
Age, continuous	0.92 (0.86–0.98)	0.89 (0.82–0.97)	0.89 (0.80–0.99)
Focal epileptiform	7.18 (0.89–57.63)		73.36 (1.75–3075.25)
Race	2.78 (0.61–12.6)	7.35 (1.42–37.98)	2.66 (0.39–18.36)
Severity	2.63 (0.71–9.72)	4.15 (1.06–16.27)	3.42 (0.72–16.11)
Hypertension[a]	0.24 (0.03–1.83)	0.34 (0.04–2.84)	0.67 (0.07–6.39)
Depression	0.45 (0.15–1.40)	0.48 (0.15–1.58)	0.23 (0.05–1.18)
Duration, continuous[a]	1.16 (1.00–1.35)	1.13 (0.97–1.31)	1.00 (0.82–1.22)
Education, continuous[a]	1.06 (0.90–1.35)		
Slow dominant rhythm	0.25(0.03–1.98)		0.14 (0.01–1.45)

[a]In the reported multivariate models, a variable was included in the model if its risk ratio was strong, as defined in the Methods section, or the variable confounded age.

whereas a history of hypertension, depression (based on Hamilton score), and slow dominant EEG rhythm were protective.

A confounder is an independent risk factor for the disease (unprovoked seizures) but is also associated with another independent risk factor for the disease. When evaluating potential confounders with age, which had the strongest overall effect, we found that race, duration, hypertension, focal epileptiform findings, and slow dominant rhythm all were confounded by and confounding age. The predictive effect of younger age was enhanced by race and duration. Hypertension, which was protective, was less so in younger subjects. The increased risk of seizures in more severely demented patients was heightened when patients were younger. Depression increased risk of seizures at a younger age. These confounders were included in the multivariate models as appropriate.

In multivariate models, presented in Table 2, the point estimates maintained univariate directions. For the entire cohort, younger age (RR, 0.89; 95% CI, 0.82–0.97; $p = 0.01$), African-American ethnic background (RR, 7.35; 95% CI, 1.42–37.98; $p = 0.02$), and greater dementia severity (RR, 4.15; 95% CI, 1.06–16.27; $p = 0.04$) were predictive of incident seizures ($p < 0.05$). Education dropped out of the model.

Multivariate analyses including EEG findings were performed in the subsample who had EEGs (nine incident seizures in 114 individuals included in the multivariate model with data for all variables), with similar findings (Table 2). However, African-American ethnic background (RR, 2.66; 95% CI, 0.39–18.36) was no longer significant. Focal epileptiform findings were predictive of seizures (RR, 73.36; 95% CI, 1.75–3075.25; $p = 0.02$).

Race

The cumulative incidence of seizures in African Americans was nearly 18% by 7 years. Because the high incidence of unprovoked seizures in African Americans may have influenced overall results, we looked at whites independently. Too few African Americans (15) were in the group for multivariate modeling.

After excluding the African Americans, the eight Hispanics and one participant who declined to identify herself as white, African American, or Hispanic, univariate regressions were performed for whites alone (10 incident seizure cases in 209 white subjects). In whites, younger

TABLE 3. *Cox regression models of seizure predictors in AD: whites only*

	Univariate RR (95% CI)	Multivariate without EEG variables RR (95% CI)	Multivariate with EEG variables RR (95% CI)
Age, continuous	1.11 (1.02–1.20)	1.11 (1.03–1.20)	1.11 (1.00–1.23)
Focal epileptiform (0 whites with focal epileptiform findings)			
Severity	2.20 (0.57–8.52)	3.49 (0.86–14.21)	2.38 (0.47–11.95)
Hypertension[a]	0.31(0.03–2.45)	0.53 (0.06–4.58)	0.90 (0.09–9.19)
Depression	0.45 (0.13–1.56)	0.40 (0.11–1.42)	0.23 (0.05–1.18)
Duration, continuous[a]	1.07 (0.88–1.30)	1.05 (0.87–1.27)	0.96 (0.76–1.22)
Education, continuous[a]	1.09 (0.91–1.30)		
Slow dominant rhythm	0.33 (0.04–2.87)		0.20 (0.02–1.84)

[a]In the reported multivariate models, a variable was included in the model if its risk ratio was strong, as defined in the Methods section, or the variable confounded age.

age was predictive (RR, 1.11; 95% CI, 1.02–1.20; p = 0.01) of unprovoked seizures (Table 3). Factors included in the overall analysis were evaluated for whites alone. Most were no longer significant, although the direction of the effect remained.

DISCUSSION

Our analysis replicated the observation of earlier studies (1–3) that an increased risk for unprovoked seizures exists in individuals with AD compared with others of the same age. This supports the notion that seizures can be a part of the natural history of AD. A recent review and articles cited seizure frequencies ranging from 5 to 67% in AD (9–12). In our study, we found the incidence ratios compared with those in a reference population ranged from 87 to 3, respectively, for the youngest to the oldest group, which is a minimal estimate, as the reference population included people with AD (8).

A yearly unprovoked seizure incidence of nearly 1%, regardless of years from study entry, was also shown. One should not conclude from this linear relation that seizures occur during all stages of the disease. Duration of AD does not necessary correlate with severity of illness. Worse cognitive performance (as defined by MMSE scores) in the early stages of AD predicted later unprovoked seizures, however.

Earlier work (2) did not find younger age at AD onset to be associated with increasing risk of incident seizure, but these results are not directly comparable because the analytic approaches differed. These researchers compared the mean age at onset of patients with and without seizures, whereas we used the survival approach. In this cohort, it has been shown that younger people have more rapid disease progression (13). This supports the notion that unprovoked seizures are associated with younger age at onset because this group has a more rapid decline.

The racial findings are difficult to interpret because of the small number of African Americans in this cohort. Few data are relevant to AD or seizures in African Americans (14). Therefore we can not address in this data set whether the nearly doubled cumulative incidence of unprovoked seizures in the African-American group is specific to AD, is reflective of a greater incidence of seizures in elderly African Americans, or is an artifact of small sample size.

Depression and hypertension have been identified as a risk factors for unprovoked seizures (15–18). In this analysis of people with mild-to-moderate AD, neither depression nor hypertension increased the risk for seizures. The observation of a protective effect of hypertension against seizures in AD requires further confirmation.

Because EEGs were not required at study entry, it is possible that the selection of cases receiving EEGs may have been biased by undetermined factors. We think that this is not the case because the other variables remained similar in models with and without EEG variables. We conclude that the presence or an absence of an EEG at baseline simply reflected the clinical practice of the personal physicians of the subjects enrolled in the Predictors study, and no selection bias was present. It appears that an epileptiform EEG is strongly predictive of unprovoked seizures.

We chose not to evaluate the cohort for epilepsy (recurrent unprovoked seizures) because some patients received medications after a first seizure. Neither did we evaluate seizure type because insufficient detail was present in the data for accurate categorization. Because we reviewed the study charts and medical records of these seizure patients, we can say that these were not acute symptomatic seizures (19).

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