

New-Onset Epilepsy Risk Factors in Older Veterans

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OBJECTIVES: To identify risk factors for new-onset geriatric epilepsy that may trigger clinicians to consider a differential diagnosis of epilepsy at symptom onset.

DESIGN: Retrospective cohort study.

SETTING: National Veterans Affairs (VA) databases.

PARTICIPANTS: Veterans aged 66 and older in fiscal year 2000 (FY00) who received VA care in FY99 and FY00. Individuals with new-onset epilepsy based on a validated algorithm constituted the epilepsy cohort (n = 1,843), and individuals without epilepsy constituted the geriatric cohort (n = 1,023,376).

MEASUREMENTS: Age, sex, and race were derived from VA databases. Clinical conditions associated with new-onset geriatric epilepsy (e.g., cerebrovascular disease, dementia, brain tumor) and stroke risk-factors (e.g., hypertension, diabetes mellitus, cardiovascular disease) were identified using validated International Classification of Diseases, Ninth Revision, Clinical Modification, codes before epilepsy onset (epilepsy cohort) and in FY00 (geriatric cohort).

RESULTS: Multivariable logistic regression analysis indicated that patients with cerebrovascular disease (odds ratio (OR) = 3.50, 95% confidence interval (CI) = 3.13–3.91), cerebrovascular disease and dementia (OR = 4.14, 95% CI = 3.46–4.96), brain tumor (OR = 2.14, 95% CI = 1.46–3.13), head injury (OR = 2.11, 95% CI = 1.41–3.14), and other central nervous system (CNS) conditions (OR = 1.57, 95% CI = 1.32–1.88) were more likely to experience new-onset epilepsy. Statin prescription (OR = 0.64, 95% CI = 0.56–0.73), older age (≥ 85 vs 66–74, OR = 0.66, 95% CI = 0.50–0.87), obesity (OR = 0.74, 95%

CI = 0.62–0.87), and hypercholesterolemia (OR = 0.87, 95% CI = 0.76–0.98) were associated with a lower likelihood of epilepsy.

CONCLUSION: These data suggest greater epilepsy risk for older individuals with CNS insult and an additive effect of cerebrovascular disease and dementia. The statin finding requires further exploration but points to a possible target for prevention of geriatric epilepsy. *J Am Geriatr Soc* 57:237–242, 2009.

Key words: epilepsy; risk factors; cohort study; race; aged

Although many consider epilepsy to be a condition of childhood, the highest incidence of new-onset epilepsy occurs in individuals aged 60 and older, and it is anticipated that elderly people will constitute half of all new-onset epilepsy patients by 2020.¹ Epilepsy is costly² and has a profound effect on older patients' self-reported quality of life, change in health status over the course of a year, and activity level.³ Despite this growing problem, making an accurate diagnosis in elderly people is clinically challenging, as evidenced by a delay, on average, of 1.7 years from the time of initial symptoms to the official diagnosis and treatment of epilepsy.⁴ This delay is due in part to the fact that older patients do not present with typical features of complex partial seizures (CPSs), the most common type of seizures in this population.⁵ Older patients rarely describe an aura or have automatisms—features that are common in younger patients with CPS.⁶ Moreover, they have prolonged postictal confusion, lasting hours to days to weeks rather than the more-typical 5- to 15-minute postictal period in younger patients. A disturbance of consciousness followed by a blank stare may be the only sign of seizure in older patients. This study identified geriatric epilepsy risk factors, which may indicate to clinicians the possibility that an older patient who presents with blackout spells, altered mental status, or confusion may have epilepsy early in the process of examining differential diagnoses.

Cerebrovascular disease, dementia, tumor, and head trauma are the most frequently identified central nervous

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system (CNS) disorders associated with new-onset epilepsy in elderly people,⁷⁻⁹ but some researchers have recently proposed that CNS microvascular disease is the cause of most of the cryptogenic cases in which the exact cause is unknown, because systemic cerebrovascular disease risk factors (hypertension, hypercholesterolemia, coronary artery disease, and peripheral vascular disease) have been associated with seizures in the absence of evidence of stroke on neuroimaging studies.^{10,11} To determine whether only CNS disease or both CNS disease and cerebrovascular risk factors raises the risk of epilepsy, it is important to include them simultaneously in a multivariable model to see the effects of each type of risk factor, independent of the others.

This study used national Department of Veterans Affairs (VA) databases to identify risk factors for geriatric epilepsy by comparing patient characteristics in older individuals with new-onset epilepsy with those of a similar seizure-free cohort. By including CNS risk factors and systemic diseases associated with those CNS risk factors, the hypothesis that the systemic diseases are independent risk factors for new-onset epilepsy in elderly people even after controlling for cerebrovascular disease, dementia, brain tumor, and head injury was tested.

METHODS

Data

After approval from institutional review boards at the University of Texas Health Science Center at San Antonio and the Bedford and Hines VA Medical Centers, the cohorts were identified using national VA databases.

Population and Setting

All veterans aged 66 and older at the beginning of fiscal year 2000 (FY00; October 1, 1999–September 30, 2000) who received VA care in FY99 and FY00 were identified using national VA inpatient, outpatient, and pharmacy data. Individuals who had new-onset epilepsy during FY00 based on a previously validated algorithm¹² were classified as the Treatment In Geriatric Epilepsy Research (TIGER) cohort. In brief, epilepsy patients were identified as those who received an antiepileptic drug (AED) from the VA outpatient pharmacy in FY00 and who also had a diagnosis of epilepsy (345.XX) or convulsion (780.39) in the VA inpatient, outpatient, or Medicare databases in FY99 to FY00. From this epilepsy population, patients with new-onset epilepsy (TIGER cohort) were identified as those with a first diagnosis of epilepsy and new AED treatment in FY00. Validation of this algorithm is described elsewhere.¹³ Patients with a previous diagnosis of epilepsy or who had a first diagnosis of epilepsy in FY00 but did not have pharmacy data available for the prior year were excluded from all analyses, because the onset of epilepsy could not be estimated. Individuals who received VA care in FY99-00 and who did not meet criteria for epilepsy constituted the geriatric cohort. Although Medicare data were used to identify patients with epilepsy for the TIGER study, they were not available for the geriatric cohort. Accordingly, only VA data were used to identify demographic characteristics (age, sex, race) and comorbid conditions for the purposes of this study.

Measures

Validated International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code algorithms and national VA data inpatient and outpatient databases (FY98-00) were used to identify comorbid conditions cited as possible CNS risk factors associated with epilepsy in epidemiological studies (e.g., stroke, dementia, brain tumor, head injury)^{7,8} and other systemic conditions that increase risk of cerebrovascular disease (e.g., hypertension, diabetes mellitus, cardiovascular disease). These conditions were identified through the end of FY00 for the geriatric cohort and before the first epilepsy diagnosis in FY00 for the TIGER cohort. Because of an unanticipated finding for hypercholesterolemia, individuals who received lipid-lowering medications were also identified. Individuals who received 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors were classified as receiving statins; individuals receiving other lipid-lowering medications were classified as such.

Analysis

Cohort comparisons of demographic characteristics are presented first, followed by comparisons of specific comorbid conditions. Differences between groups were identified using the chi-square statistic with a significance level set at $P < .002$ because of the large sample size and large number of comparisons.¹⁴ Logistic regression analyses predicting epilepsy were then conducted using previously identified epilepsy risk factors and comorbid conditions associated with those risk factors. The only variable with objectively missing data was race (19%). These individuals were excluded in the multivariable analyses, although results of analyses using the race category “missing” were nearly identical. Interactions between the primary epilepsy risk factors were included; only interactions that were significant in the final model were included. The C statistic was used to assess model fit,¹⁵ and model assumptions were also checked by assessing the proportional odds. Analyses were conducted with SAS version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Table 1 shows descriptive statistics for the TIGER and geriatric cohorts. These data suggest that blacks were more likely to be represented in the TIGER cohort than the geriatric cohort (17.6% vs 9.3%), which may be due to differential rates of missing race data between the geriatric and epilepsy cohorts (19.6% vs 12.6%). Table 1 also demonstrates that there were significant differences between the cohorts with regard to CNS and systemic risk factors for epilepsy. Individuals in the TIGER cohort were significantly more likely than those in the geriatric cohort to have previous diagnoses of cerebrovascular disease, dementia, brain tumor, and recent head injury. CNS disorders (e.g., Parkinson's disease, multiple sclerosis), cardiovascular disease (congestive heart failure, cardiac arrhythmias, myocardial infarction, valvular heart disease), peripheral vascular disease, hypercholesterolemia, and alcohol abuse or dependence were also more likely in the TIGER cohort in bivariate analysis. Individuals in the geriatric cohort were more likely to have diagnoses of obesity and hypercholesterolemia.

Because cerebrovascular disease and dementia were so common in both cohorts, and the interaction between

Table 1. Demographic and Clinical Characteristics of the Treatment In Geriatric Epilepsy Research (TIGER) and Geriatric Cohorts

Characteristic	TIGER Cohort	Geriatric Cohort
	n = 1,843	n = 1,023,376
n (%)		
Age		
65–74	966 (52.4)	558,661 (54.6)
75–84	818 (44.4)	430,125 (42.0)
≥85	59 (3.2)	34,590 (3.4)
Sex		
Female	30 (1.6)	20,570 (2.0)
Male	1,813 (98.4)	1,002,806 (97.9)
Race*		
Black	324 (17.6)	94,662 (9.3)
White	1,204 (65.3)	683,615 (66.8)
Hispanic	83 (4.5)	44,619 (4.4)
Unknown	232 (12.6)	200,479 (19.6)
CNS risk factors		
Stroke*	700 (37.9)	151,971 (14.9)
Dementia*	308 (16.7)	67,236 (6.6)
Brain tumor*	29 (1.6)	5,833 (0.6)
Head injury	26 (1.4)	3,805 (0.4)
Other CNS disorders*	160 (8.7)	36,842 (3.6)
Systemic cerebrovascular risk factors		
Cardiovascular disease*	674 (36.6)	312,334 (30.5)
Peripheral vascular disorders*	363 (19.7)	164,150(16.0)
Hypertension*	1,389 (75.4)	734,477 (71.8)
Diabetes mellitus	566 (30.7)	301,487 (29.5)
Obesity*	181 (9.9)	137,542 (13.4)
Hypercholesterolemia*	638 (34.6)	434,628 (42.5)
Alcohol abuse or dependence*	130 (7.1)	42,470 (4.2)
Lipid-lowering drugs		
Statins*	393 (21.3)	310,390 (30.3)
Other	49 (2.7)	37,763 (3.7)

* $P < .001$.
CNS = central nervous system.

cerebrovascular disease and dementia was significant in multivariable analyses, a breakdown of patients with different combinations of cerebrovascular disease and dementia is provided in Table 2. These data demonstrate that patients in the geriatric cohort were significantly less likely to have cerebrovascular disease or dementia and that patients in the TIGER cohort were more likely to have all combinations of cerebrovascular disease and dementia (all $P < .001$).

Table 3 shows results of the logistic regression analysis examining risk factors for epilepsy in the older veteran cohorts. Demographic characteristics associated with epilepsy included age and race. The oldest old were less likely than those aged 66 to 74 to have new-onset epilepsy. Blacks were more likely to have a new epilepsy diagnosis than whites. As expected, patients with all combinations of cerebrovascular disease and dementia were at significantly higher risk of epilepsy. Patients with a prior diagnosis of cerebrovascular

Table 2. Combinations of Cerebrovascular Disease and Dementia in Older Veterans

Variable	Treatment In Geriatric Epilepsy Research Cohort	Geriatric Cohort
	n = 1,843	n = 1,023,376
n (%)		
Neither cerebrovascular disease nor dementia*	993 (53.9)	828,730 (80.9)
Dementia only*	150 (8.1)	42,675 (4.2)
Cerebrovascular disease only*	542 (29.4)	127,410 (12.5)
Cerebrovascular disease and dementia*	158 (8.6)	24,561 (2.4)

* $P < .001$.

disease and dementia were four times as likely to have epilepsy as their counterparts with neither condition. Individuals with brain tumor, head injury, and other CNS conditions were also more likely to have a new epilepsy diagnosis than those without these conditions.

The effects of cardiovascular disease, hypertension, and peripheral vascular disease were not significant once the effects of primary risk factors were controlled. Hypercholesterolemia and obesity were associated with a slightly

Table 3. Logistic Regression: Risk Factors for New-Onset Epilepsy in Older Veterans

Risk Factor	Odds Ratio (95% Confidence Interval)
Age (vs 65–74)	
75–84	0.92 (0.83–1.02)
≥85	0.66 (0.50–0.87)
Female (vs male)	
	0.79 (0.52–1.18)
Race (vs white)	
Black	1.75 (1.54–1.98)
Hispanic	1.03 (0.82–1.29)
CNS risk factors	
Stroke and dementia (vs no stroke or dementia)	
Dementia only	2.31 (1.91–2.79)
Stroke only	3.43 (3.05–3.86)
Stroke and dementia	4.04 (3.36–4.87)
Brain tumor	2.14 (1.46–3.13)
Head injury	2.11 (1.41–3.14)
Other CNS conditions	1.57 (1.32–1.88)
Risk factors for stroke and dementia	
Cardiovascular disease	1.11 (1.00–1.23)
Hypertension	1.04 (0.92–1.17)
Peripheral vascular disease	0.92 (0.82–1.05)
Diabetes mellitus	0.97 (0.87–1.08)
Obesity	0.74 (0.62–0.87)
Hypercholesterolemia	0.87 (0.76–0.98)
Alcohol abuse or dependence	1.26 (1.04–1.51)
Lipid-lowering drugs	
Statins	0.65 (0.56–0.75)
Other	0.84 (0.62–1.14)

CNS = central nervous system.

lower risk of epilepsy in this population. Because treatment of hypercholesterolemia with statin drugs has been associated with lower risk of subsequent nonhemorrhagic stroke,¹⁶ two additional variables—prescription of statins and of other lipid-lowering agents—were included in the model. This resulted in an attenuated, but still significant, effect for hypercholesterolemia and a significantly lower likelihood of epilepsy for patients prescribed statins (Table 3).

DISCUSSION

This study examined potential CNS and systemic risk factors associated with new-onset epilepsy in elderly people. Using national VA databases, older (66 and older) veterans with new-onset epilepsy were compared with a similar geriatric cohort while controlling for independent, potentially confounding, patient variables. Only CNS conditions and systemic illnesses that were recognized before the diagnosis of epilepsy were examined in these models.

Consistent with the few studies examining epilepsy incidence according to race and age,¹⁷ older black men were at higher risk of epilepsy than older white men, even after controlling for CNS and systemic diseases that are more prevalent in blacks, such as cerebrovascular disease, cardiovascular disease, and hypertension. Although this finding must be interpreted with caution, because the rates of missing data for the geriatric cohort were significantly higher than for the TIGER cohort, the unpublished analyses comparing race data in VA and Medicare files suggest they are valid. Concordance of race in VA and Medicare data in a sample of patients receiving antiepileptic drugs was high for whites (96%) and blacks (89%). Of those with missing VA race data, 93% were identified as white and 4% as black in Medicare data. Analysis including the missing race group found that odds ratios (ORs) for those with missing race was lower than those of whites (OR = 0.80, 95% confidence interval = 0.69–0.92).

The multivariable analysis found a lower likelihood of epilepsy for the oldest-old than for those aged 66 to 74. Although this is inconsistent with epidemiological studies,⁵ this finding was obtained after controlling for CNS conditions that are more prevalent in the oldest-old and are associated with much greater risk.

Consistent with the literature, cerebrovascular disease and dementia had the strongest relationship with new-onset epilepsy in this cohort of older veterans.^{18–21} Moreover, individuals with cerebrovascular disease and dementia were four times as likely to have new-onset epilepsy, suggesting a previously undescribed synergistic or “additive” effect of these two CNS conditions on epilepsy risk.

Despite technological advances, the cause of new-onset epilepsy in one-third to one-half of older individuals remains unknown.^{19–22} Because it has been proposed that CNS vascular disease is the etiology of most of the “cryptogenic” cases, because systemic risk factors for cerebrovascular disease have been associated with seizures in the absence of cerebrovascular disease,^{10,11,23} systemic illnesses, including hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease and peripheral vascular disease, were examined in the two cohorts. Bivariate analyses supported the idea that cardiovascular disease, peripheral vascular disease, and hypertension were associ-

ated with subsequent epilepsy, but after controlling for underlying variables of cerebrovascular disease and dementia, systemic cerebrovascular risk factors were no longer associated with greater odds of new-onset epilepsy. This inconsistency with prior research may be due to variation in the populations studied. A previous study examined all new-onset epilepsy in adults,⁷ whereas the current study focused exclusively on the elderly population. As hypertension becomes increasingly common with age, the presence of hypertension may become less predictive of epilepsy within an elderly population. Alternatively, increasing sophistication in imaging technology has improved the ability to detect small strokes. Therefore, individuals who may previously have been identified with hypertension but no stroke may now be identified with both disease states, although it is likely that the difference in findings is due to differential methods of assessment.

Previous studies used more-traditional population-based epidemiological methods, assessing the association between individual disease states and new-onset epilepsy. The current study used a retrospective cohort design with multivariable models to assess the independent effect of multiple disease states on the risk of epilepsy simultaneously. The fact that stroke risk factors were significantly more common in the TIGER cohort than the geriatric cohort but not significant predictors of epilepsy once cerebrovascular disease and dementia were controlled for suggests that the effect of those disease states on epilepsy works through the greater risk for stroke and dementia associated with them.

Of interest is the finding that patients prescribed statin medications were less likely to develop epilepsy despite the fact that they had more medical conditions and prescribed medications. Statins are known to significantly decrease the risk of myocardial infarction and nonhemorrhagic stroke,^{16,24} and these findings suggest that they may play a role in slowing or preventing the development of epilepsy in elderly people. This may be due to an inability to completely control for statins' protective effects against prior stroke^{25,26} or their well-documented effects on vasculature, including plaque stabilization, antioxidant effects, and nitric oxide balance.²⁷ This finding must be interpreted in light of several things. First, some might argue that this finding may be the result of a “healthy user effect,” in which people who were prescribed and filled statin prescriptions may be more likely to exhibit other healthy behaviors such as receiving annual physicals or other preventive care. Other lipid-lowering drugs were included in the model to assess this potential bias, because they are similar to statins but have different mechanisms of action, but no significant effect was found. Second, the pharmacy database provides information only on the prescriptions received by the patient; assessment of medication adherence and efficacy were not determined.

This study also found a counterintuitive effect for obesity and hypercholesterolemia, in which individuals with a diagnosis of obesity or hypercholesterolemia were less likely to have a new-onset epilepsy diagnosis than those without such a diagnosis. Although this effect size was not large, it is consistent with a growing body of literature describing an “obesity paradox” in patients with known cardiovascular disease.²⁸ The recent report that metabolic

syndrome is associated with slower cognitive decline in patients aged 85 to 90 raises the issue that being overweight may be neuroprotective in certain individuals.²⁹ As with the findings regarding statin prescriptions, this must be interpreted with caution, because no additional information regarding weight or body mass index was available in the study population, and diagnoses of obesity are underreported.³⁰

Several additional potential limitations exist. First, this study used administrative data to identify a cohort of older patients with new-onset epilepsy. Although some concern may arise about identification of epilepsy using the more general convulsion diagnosis (ICD-9-CM code 780.39), chart abstraction revealed that these were accurately identified as new-onset epilepsy, because the algorithm also required new use of an AED within 1 year of the initial seizure diagnosis.¹³ Nevertheless, it is possible that individuals who received AEDs from non-VA sources were misclassified in the geriatric cohort. Because the prevalence (1.8%) and incidence (0.17%) were similar to those found in other epidemiological studies, the likelihood of misclassification was small. It is also possible that some patients with non-epileptic episodes resembling seizures (e.g., psychogenic seizures) might inadvertently have been included in this sample.^{1,31} If so, the findings would be biased toward the null, suggesting that the results of the current study were a conservative estimate. In addition, the findings were based on data from a predominately male cohort, so they may not generalize to the geriatric population in the United States, particularly to women.

In conclusion, the results confirm earlier reports that stroke and dementia are the most common CNS risk factors for the development of epilepsy and suggest that people with both stroke and dementia are at even greater risk of new-onset epilepsy.^{32–34} In contrast to previous research, cerebrovascular risk factors were not associated with an independent risk of epilepsy in elderly people.¹¹ The data suggest that, at least for elderly men, the association between hypertension and other cardiovascular diseases and epilepsy is primarily through the greater risk for stroke and dementia. Recognition of these risk factors for epilepsy may lead clinicians to consider epilepsy early in the differential diagnosis of an older patient presenting with blackout spells, altered mental status, or confusion—common symptoms of complex partial seizures in older patients. The potential protective mechanism of statins and obesity require further exploration but may be examined as future targets for geriatric epilepsy prevention.

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