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Patients with epilepsy are at an increased risk of subsequent stroke: A population-based cohort study

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ABSTRACT

Purpose: Epilepsy is well known as a disorder in poststroke patients. However, studies that have investigated the association between epilepsy and the risk of subsequent stroke are limited. This population-based study investigated the incidence and risk of stroke in patients with epilepsy by using the Taiwan National Health Insurance claims data.
Methods: We identified 3812 patients newly diagnosed with epilepsy in 2000–2008 and 15,248 nonepilepsy comparisons frequency matched according to sex, age, and index year. We searched for subsequent stroke diagnoses in both cohorts until the end of 2009. The incidence rates and hazard ratios of stroke were estimated based on sex, age, the average defined daily doses (DDDs) of antiepilepsy drugs, and comorbidity.
Results: The stroke incidence of the epilepsy cohort was 3-fold higher than that of the comparison cohort. The age-specific results indicated that in the epilepsy cohort and the comparison cohort, the risk was the highest for the youngest group (20–39 years).
Conclusion: The patients with epilepsy exhibited a higher incidence of cerebral stroke than the general population did. In addition, younger patients with epilepsy and patients who took a high doses of antiepileptic drugs exhibited a high risk of stroke.

1. Introduction

Previous studies have determined that patients with epilepsy developed a wider range of medical and neurologic disorders, compared with the general population.[1,2] The comorbidities include somatic disorders, such as cardiac, gastrointestinal, and respiratory disorders, metabolic and endocrine disorders, stroke, dementia, and migraines.[3–7] Numerous epidemiological studies have reported that patients with epilepsy exhibited a higher mortality rate than did the general population. Stroke was one of the major fatal causes.[8–11]

Using certain antiepileptic drugs (AEDs) has been associated with an increased risk of atherosclerosis,[12] suggesting that these drugs could be responsible for increased cardiovascular risk in patients with epilepsy.[13] According to a review of relevant literature, we concluded that patients with epilepsy are at a higher risk of stroke than the general population is.[14,15] However, previous studies might have been limited by a cross-sectional design, small sample sizes, or confounding effects.

Epilepsy is well known as a disorder in poststroke patients.[16–18] Studies that have investigated the association of epilepsy with the risk of subsequent stroke are limited.[3,5] This study used the UK General Practice Research Database, which indicated a relative

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hazard of 2.89 for stroke in patients presenting with seizers in late-life.[5] The risk remains unclear regarding young patients with epilepsy.

We used the National Health Insurance (NHI) Research Database to evaluate the risk of stroke among adult patients with epilepsy in a 10-year follow-up period. This population-based retrospective cohort study addressed the epilepsy-cerebral stroke link, considering the associations with sex, age, the average defined daily doses (DDDs) of antiepilepsy drugs, and comorbidities.

2. Methods

2.1. Data source

Taiwan officially commenced the NHI program in March 1995, providing universal health insurance to 99% of the population and 92% of the medical institutions in Taiwan were included in the system.[19–21]

This study used the Longitudinal Health Insurance Database, which includes historical claims data from 1996 to 2009 for 1 million people randomly sampled by the National Health Research Institute (NHRI) from the entire insured population registered in 2000. Disease diagnoses were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for the diagnosis of disease. The outpatient claims data consisted of 3 diagnoses, and the inpatient claims data consisted of 5 diagnoses, accompanied by detailed pharmaceutical prescriptions and treatment procedures. The NHRI scrambled patient identifications and used surrogate numbers to secure patient privacy. The present study was approved by the ethics committee at China Medical University and Hospital.

2.2. Study population

To increase the validity of the diagnoses, we selected patients newly diagnosed with epilepsy in 2000–2008 (ICD-9-CM, code 345), who were prescribed antiepileptic drugs, as the epilepsy cohort.[18] The index date of the epilepsy cohort was set as the epilepsy diagnosis date. Patients in the comparison cohort were randomly selected from individuals who were free from epilepsy in 1996–2008 and frequency matched according to sex, age (per 5 years), and all comorbidities, except for atrial fibrillation (AF) (AF was not included in the frequency criteria because of low AF prevalence in individuals without epilepsy; however, the proportion of AF in the epilepsy cohort was 2.0%, and that in the comparison cohort was 1.0%), yielding a 4-fold sample size. The index date for the comparison cohort was randomly assigned the same month and day as the index year of the matched case. The follow-up time was terminated on the date of stroke event diagnosis, withdrawal from the insurance program, or on December 31, 2009. The event of interest in the study was a subsequent new stroke event (ICD-9-CM 430–438), which was determined by brain imaging, that was identified using the inpatient file. We also distinguished the stroke events as either ischemic strokes (ICD-9-CM 433–438) or hemorrhagic strokes (ICD-9-CM 430–432), excluding stroke patients aged less than 20 years.

We also calculated the average DDDs of AEDs in the epilepsy cohort as the total sum of AEDs used during the observation time divided by the total follow-up duration (DDD/year). The AEDs were phenytoin (ATC code: N03AB02), carbamazepine (ATC code: N03AF01), gabapentin (ATC code: N03AX12), levetiracetam (ATC code: N03AX14), oxcarbazepine (ATC code: N03AF02), tiagabine (ATC code: N03AG06), topiramate (ATC code: N03AX11), vigabatrin (ATC code: N03AG04), phenobarbital (ATC code: N03AA02), and valproate (ATC code: N03AG01). The epilepsy cohort was recategorized into 3 subcohorts according to the tertile cutpoint of the average DDDs.

Information on potential confounders, such as demographic factors or the comorbidity of stroke, were also collected in this study. The comorbidities used in this study were hypertension (ICD-9-CM 401–405) and hyperlipidemia (ICD-9-CM 272), both of which were diagnosed at least 3 times; diabetes mellitus (DM)(ICD-9-CM 250), diagnosed at least 2 times; coronary artery disease (CAD)(ICD-9-CM 410–413, 414.0, 414.8, and 414.9); and AF (ICD-9-CM 427.3), diagnosed once.

2.3. Statistical analysis

We used Chi-square tests to examine the categorical variables and t tests to examine the continuous variables to compare the characteristics between the epilepsy and comparison cohorts. The incidence of stroke in the 2 groups was determined. Compared with the comparison cohort, the hazard ratio (HR) and 95% confidence interval (CI) of stroke for the epilepsy cohort were estimated using the Cox proportional hazards regression model after adjusting for AF. The Kaplan–Meier method was used to evaluate the stroke-free curves of stroke for the epilepsy and comparison cohorts, and the variations in the curves were examined using logrank tests.

Statistical analysis and data management were performed using the Statistical Analysis System (SAS) 9.3 (SAS Institute Inc., Cary, NC, USA), and the survival curve was determined using R 2.13.0 (The R Foundation for Statistical Computing, Vienna, Austria). A P value less than 0.05 was considered significant.

3. Results

This study used 15,248 comparison individuals and 3812 patients with epilepsy, yielding a mean age of 50 years, and 41.7% of the participants were women (Table 1). Except for AF, the distribution of all the comorbidities between the epilepsy and comparison cohorts was similar ($P > .99$).

The results of using the Kaplan–Meier model shown in Fig. 1 indicated that the cumulative incidence of stroke for the epilepsy cohort was significantly higher than that for the comparison cohort (logrank test < 0.0001). The incidence of stroke was approximately 3-fold higher in the epilepsy cohort than in the comparison cohort (24.08 vs. 7.96 per 1000 person-year), yielding an HR of 2.92 (95% CI = 2.58–3.30) after adjusting for AF (Table 2). The incidence of ischemic stroke was nearly 3-fold higher than that of hemorrhagic stroke for both cohorts. Compared with the comparison cohort, the epilepsy cohort exhibited HRs of 2.85 (95% CI = 2.49–3.26) for ischemic stroke and 3.30 (95% CI = 2.46–4.43) for hemorrhagic

Table 1
Characteristic of the study population.

Variable	Comparison cohort	Epilepsy cohort	P-Value
	N = 15,248 (%)	N = 3812 (%)	
Age, mean (SD)[a]	50.0 (18.2)	50.1 (18.3)	0.9082
20–39	5116 (33.6)	1279 (33.6)	>0.99
40–59	5436 (35.7)	1359 (35.7)	
≧60	4696 (30.8)	1174 (30.8)	
Sex			>0.99
Female	6352 (41.7)	1588 (41.7)	
Male	8896 (58.3)	2224 (58.3)	
Comorbidity			
Hypertension	5540 (36.3)	1385 (36.3)	>0.99
AF	145 (1.0)	78 (2.0)	<0.0001
CAD	2084 (13.7)	521 (13.7)	>0.99
Diabetes	2284 (15.0)	571 (15.0)	>0.99
Hyperlipidemia	2916 (19.1)	729 (19.1)	>0.99

[a] t-Test.