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Original article

A high risk of hyperlipidemia in epilepsy patients: a nationwide population-based cohort study

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ABSTRACT

Purpose: This study evaluated the effect of epilepsy on the development of hyperlipidemia (HL) in Taiwan.
Methods: We conducted a nationwide population-based cohort study based on data obtained from the National Health Insurance Research Database of Taiwan. We identified 990 cases involving patients whose epilepsy was newly diagnosed between 2000 and 2005, and we also selected a comparison cohort comprising 3960 patients without epilepsy. Cox proportional hazards regression models were used to examine the association between epilepsy and HL.
Results: The mean follow-up period was 6.63 years for the epilepsy cohort and 7.49 years for the comparison cohort. The incidence rate of HL was 1.28-fold higher in the epilepsy cohort than it was in the comparison cohort (34.14 vs. 26.96 per 1000 person-years), with an adjusted hazard ratio of 1.17 (95% confidence interval, 1.01–1.36) after adjusting the model to account for the effects of sex and comorbidities. The most at-risk patients were those aged 50 to 59 years (hazard ratio, 1.35; 95% confidence interval, 1.04–1.79). For the epilepsy patients, the combined effect of ischemic heart disease, hypertension, and diabetes was associated with a significantly higher risk of developing HL compared with the patients with neither epilepsy nor any comorbidity.
Conclusions: Middle-aged epilepsy patients are at a significantly higher risk of developing HL. The results could assist in explaining the high risk of cerebral and cardiac vascular disease in epilepsy patients.

Introduction

Epilepsy is a well-recognized brain disease affecting 0.5% to 1.0% of people worldwide [1,2]. The pathogenesis of epilepsy indicates that it is of idiopathic origin or it manifests as symptomatic epilepsy after an insult to the brain. Among the many causes of symptomatic epilepsy in adults, the three major ones are head injury, stroke, and brain tumor [3]. A recent study reported a year-standardized mortality ratio of 2.5 for all-cause mortality among epilepsy patients relative to that of the general population in Taiwan [4]. Both symptomatic and idiopathic epilepsies have been associated with an increased risk of ischemic heart disease (IHD) and cerebrovascular accident (CVA) in adults [5–8]. IHD and CVA are the major causes of mortality in epilepsy patients who develop vascular disease before epilepsy [9]. Animal models of epilepsy have provided strong support for cardiac mechanisms in sudden unexpected death in epilepsy through histologic evidence of myocardial ischemia after an epileptic seizure [10]. However, the involved pathogenesis and mechanism linking epilepsy and vascular disease remains unclear. Therefore, we conducted a nationwide population-based study by analyzing time series data obtained from the National Health Insurance Research Database (NHIRD) of Taiwan to determine whether the risk of developing hyperlipidemia

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All authors state that they have no conflicts of interest.

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(HL) is higher in epilepsy patients, and whether epilepsy and elevated risks of IHD and CVA in patients could be linked by means of HL.

Methods

Data sources

The NHIRD was obtained from the National Health Research Institutes. In March 1995, the Taiwanese government launched the National Health Insurance (NHI) program. By the end of 2009, the NHI program provided insurance coverage for approximately 99% of the national population (approximately 23.74 million people). The NHIRD contains the personal data of enrollees, including their sex, date of birth, outpatient and inpatient history, and records of all diagnosed diseases, which are coded in accordance with the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). To protect the privacy of enrollees, all Taiwanese citizens are assigned a unique personal identification number that can be used to link all NHI data sets without revealing any personal information. All personal identification numbers are cryptographically scrambled to ensure patient anonymity. This study was approved by the Institutional Review Board of China Medical University, Taiwan (CMU-REC-101-012).

Study participants

We identified 5012 patients with a history of epilepsy and repetitive seizures (ICD-9-CM Code 345.xx) in the registry of ambulatory and inpatient claims data from 2000 to 2005. Patients were excluded if they were aged younger than 40 years ($n = 2338$), had been a previous diagnosis of HL (ICD-9-CM Code 272.xx) ($n = 967$) or stroke (ICD-9-CM Codes 430.xx–438.xx) ($n = 576$), or were followed up for less than 1 year ($n = 141$). For each epilepsy patient in the epilepsy cohort, we randomly selected four patients from the NHIRD and assigned them to the comparison cohort. Enrollees with no history of epilepsy, HL, or stroke were frequency matched by age (per 5 years), sex, and index-year. Overall, the epilepsy and comparison cohorts comprised 990 and 3960 enrollees, respectively.

Measurements

The demographic factors examined in this study were age and sex. Patients were categorized by age into three groups: 40 to 49, 50 to 59, and ≥60 years. We considered IHD (ICD-9-CM Codes 410.xx–414.xx), hypertension (ICD-9-CM Codes 401.xx–405.xx), and diabetes (ICD-9-CM Code 250.xx) as comorbidities that were potential confounders in the association between epilepsy and HL.

The main outcome (occurrence of HL) was determined by linking ambulatory and inpatient care data. All patients were observed from the index date until the date of HL diagnosis, withdrawal from the NHI program, or December 31, 2011 (whichever occurred first).

Statistical analysis

The distribution of sociodemographic status and comorbidities between patients with and without epilepsy were analyzed using a χ^2 test for categorical variables and t test for continuous variables. The sex-, age-, and comorbidity-specific incidence density rates of HL were calculated for the follow-up period until December 31, 2011, the date of HL diagnosis, death, or loss to follow-up. Patients who had less than 1 year of follow-up were excluded from the analysis. We used the Kaplan–Meier (K–M) estimation method to plot the cumulative incidence curves of HL for both cohorts. Subsequently, we performed a log-rank test to check for statistically significant differences between the K–M curves. Cox proportional hazards models were used to assess the independent effects of epilepsy by adjusting the model to account for the effects of other variables in the models. We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting the models to account for the effects of age, sex, and comorbidities. All statistical analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC), with the significance level set to $P < .05$ for a two-tailed test.

Results

The mean age of the 990 patients in the epilepsy cohort was 57.25 years (standard deviation = 13.32) and that of the 3960 patients in the comparison cohort was 56.91 years (standard deviation = 13.53). The mean follow-up period was 6.63 years for the epilepsy cohort and 7.49 years for the comparison cohorts. Table 1 shows the baseline demographic factors and comorbidities of the study participants according to epilepsy status. The distribution of age and sex at entry were the same in both cohorts. The epilepsy cohort exhibited a higher prevalence of IHD (19.39% vs. 12.85%), hypertension (41.62% vs. 25.91%), and diabetes (5.29% vs. 5.98%) compared with the patients without epilepsy.

Figure 1 presents the cumulative incidence curves of HL according to epilepsy status. We conducted a log-rank test to compare the cumulative incidence of HL between the two cohorts and observed a significantly higher HL incidence in the epilepsy cohort ($P < .001$).

The incidence rate and HR for HL were calculated according to epilepsy status and stratified based on demographic factors and comorbidities (Table 2). The incidence rate of HL was higher in the epilepsy cohort than it was in the comparison cohort (34.15 vs. 26.96 per 1000 person-years), and the HR was 1.17 (95% CI, 1.01–1.36) after adjusting the model to account for the effects of age, sex, and comorbidity. The adjusted HR was considerably higher in the epilepsy cohort than that of the comparison cohort when the patients aged 50–59 years were considered (adjusted HR, 1.35; 95% CI, 1.01–1.79). For the patients with no comorbidity (i.e., without IHD, hypertension, and diabetes), the risk of developing HL was higher in the epilepsy cohort than in the comparison cohort after adjusting the multivariate model (HR, 1.27; 95% CI, 1.02–1.58). Among the patients without hypertension, those with epilepsy were more likely to develop HL compared with those without epilepsy (adjusted HR, 1.32; 95% CI, 1.08–1.61). Among the patients with diabetes, those with epilepsy were also more likely to have HL

Table 1
Baseline demographic factors and comorbidity of study participants according to epilepsy status

Characteristics	Control $N = 3960$		Epilepsy $N = 990$		P value
	n	%	n	%	
Gender					.99
Female	1668	42.12	417	42.12	
Male	2292	57.88	573	57.88	
Age, y					.99
40–49	1596	40.30	399	40.30	
50–59	812	20.51	203	20.51	
≥60	1552	39.19	388	39.19	
Mean (SD)	56.91 (13.53)		57.25 (13.32)		.48
Comorbidity					
IHD	509	12.85	192	19.39	<.001
Hypertension	1022	25.91	412	41.62	<.001
Diabetes	237	5.98	92	5.29	<.001

SD = standard deviation.