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Men with nonapnea sleep disorders have a high risk of developing subsequent epilepsy: A nationwide population-based cohort study

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ABSTRACT

Objective. This nationwide population-based cohort study evaluated the effects of nonapnea sleep disorders (NSDs) on the development of epilepsy.

Methods. We identified 63,865 patients aged ≥20 years, diagnosed with NSDs (ICD-9-CM: 307.4 or 780.5), and without coding for apnea-related sleep disorders (ICD-9-CM: 780.51, 780.53, or 780.57) during 2000–2003 as the NSD cohort. In addition, we enrolled a comparison cohort of 127,728 patients. We calculated the adjusted hazard ratio (aHR) for developing epilepsy (ICD-9-CM: 345) after adjustment for age, sex, comorbidities, and drug use. A Kaplan–Meier analysis was used to measure the cumulative incidence of epilepsy between the 2 groups until the end of 2011.

Results. The cumulative incidence of epilepsy was significantly higher in the NSD cohort than in the comparison cohort. The aHR for developing epilepsy in the NSD cohort was 1.52 (95% CI = 1.37–1.69). The risk of developing epilepsy was higher among males (aHR = 1.41) than among females. The age-stratified effects of NSDs on developing epilepsy were the highest among patients aged ≥65 years. When comorbidities and NSDs coexisted, the risk of epilepsy was specifically increased in patients having an NSD and stroke (aHR: 8.61, 95% CI: 7.43–9.98) in addition to brain tumors (aHR: 7.66, 95% CI: 5.06–11.6).

Conclusion. This study indicated that patients with NSDs have a higher risk of developing epilepsy and that the risk is much higher among men and older patients. These findings suggest that NSDs constitute a predisposing, possibly independent factor for developing subsequent epilepsy in adulthood.

1. Introduction

Both epilepsy and sleep disorders (SDs) are common neurological disorders, and either one of them can affect the quality of daily life in affected patients. Epilepsy has a prevalence of 0.5%–1% in the general population worldwide (Hauser et al., 1991; Benbadis and Allen, 2000), and epilepsy exerts a more serious effect on patients' lives than SDs do, such as the high risks of premature death from heart disease and stroke (Neligan et al., 2011; Aurlien et al., 2012). A 2.5-fold mortality risk, compared with the general Taiwanese population, was recently reported for Southern Taiwanese patients with epilepsy (Chang et al., 2012).

The causes of epilepsy indicate that the disease either has an idiopathic origin or appears as symptomatic epilepsy secondarily following a brain insult. Numerous causes lead to symptomatic epilepsy in adulthood, with the 3 major causes being head injury, stroke, and brain tumors (Annegers et al., 1996). According to current knowledge, a seizure develops from an imbalanced expression of the excitatory and inhibitory ion channels in the central nervous system (CNS). The electrophysiological instability in the cortex presents as a spike in an electroencephalogram, and the hypersynchronization of spikes may develop into an epileptic seizure. Sleep deprivation is a well-known factor for increasing seizure susceptibility and often provokes epileptic seizures (Bostock et al., 2015; Lucey et al., 2015; Schmitt, 2015).

Sleep is vital for living. SDs result in profound consequences for physiology, behavior, and daily abilities during waking hours (Ohayon, 2009). Symptoms of dyssomnia or insomnia may be temporary or chronic, depending on the type of SD. Currently, nonapnea SDs (NSDs)

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without evidence of hypoxic damage to the CNS are considered less threatening to human health. In this study, we determined whether NSDs are independent and predisposing factors that lead to adulthood epilepsy and subsequently affect the life quality and life-span of affected patients by enrolling an NSD cohort from Taiwan's nationwide population-based database.

2. Methods and materials

2.1. Data source

The Taiwan Bureau of National Health Insurance developed the National Health Insurance (NHI) program, which has been in effect since March 1995. This program offers full medical service to more than 99% of Taiwan residents (approximately 23 million). The claims data on the Taiwan NHI program constitute a large computerized database called the National Health Insurance Research Database (NHIRD). We used the Longitudinal Health Insurance Database (LHID 2000), a subset of the NHIRD, in this population-based cohort study. The LHID 2000 contains claims data on 1 million randomly selected beneficiaries from the 23 million insured individuals who registered during 1996–2011. Demographic data (such as those on birth and sex) and diagnostic data (such as the date and diagnoses of outpatient visits, and the date of admission and discharge with diagnoses) of all insured individuals are included in this database.

In our study, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were recorded by a general physician, a psychiatrist, or a neurologist and were used to define diseases and medical procedures. The NHIRD is highly representative of the general population of Taiwan because the NHI is a single-payer and universal program. All insurance claims are scrutinized by medical reimbursement specialists and subjected to peer review according to standard diagnostic criteria. In addition, physicians and hospitals are penalized for incorrect diagnoses and codes. Therefore, the diagnoses of sleep disorders, epilepsy, and comorbidities in this study are highly reliable (Cheng et al., 2011; Harnod et al., 2015).

Furthermore, the NHIRD data are anonymized for protecting personal privacy. This study was approved by the Institutional Review Board of China Medical University.

2.2. Selection of study patients

Our study enrolled 63,865 patients aged ≥20 years and newly diagnosed with NSDs (ICD-9-CM: 307.4, 780.5, excluding780.51, 780.53, and 780.57) during 2000–2003. The index date was defined as when a patient received a primary diagnosis of an NSD for the first time. Through frequency matching with age (in 5-year intervals), sex, and the index year, 2 patients without SD were randomly selected from the LHID 2000 for each patient with an NSD to form the comparison cohort (n = 127,728). Patients who developed epilepsy (ICD-9-CM: 345) before the index date and those aged <20 years were excluded.

The follow-up period was measured in both cohorts from the index date until the development of epilepsy, withdrawal from the LHID database, or December 31, 2011, which ever occurred first. Drug exposure histories in the subjects of this study were measured before the end date, and their types of exposure were categorized as zolpidem, benzodiazepine (BZD), or both.

In addition, we adjusted for comorbidities. The comorbidities were defined as diseases diagnosed before the study end date, including hypertension (ICD-9-CM: 401–405), hyperlipidemia (272), diabetes (250), anxiety (300.0, 300.2, 300.3, 308.3, and 309.81), depression (296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 3092.8, and 311), head injury (850–854, and 959.01), stroke (430–438), and brain tumors (225, 191, 192, 194.3, and 194.4).

2.3. Data analysis

The SAS 9.4 statistical package (SAS Institute Inc., NC, USA) was used for the statistical analyses, and 2-tailed $P < 0.05$ was considered significant. The baseline distribution of demographic variables and potential risk factors (history of comorbidities and drug use) in the NSD and comparison cohorts were analyzed using a chi-square test for categorical variables and a Student *t*-test for continuous variables. The incidence rates of epilepsy development in both cohorts were calculated after stratifying each variable. The incidence rate ratio (IRR) and 95% confidence intervals (95% CIs) of epilepsy were presented using the Poisson regression model. The crude hazard ratios (HRs) and 95% CIs of epilepsy in the NSD and comparison cohorts were calculated using the Cox proportional hazard regression model. After adjustment for sex, age, each comorbidity (including hypertension, hyperlipidemia, diabetes, stroke, anxiety, depression, head injury, and brain tumors), and drug use (no/yes), the association between NSDs and epilepsy was evaluated using a multivariate Cox proportional hazard model to estimate the adjusted HR (aHR) and 95% CI. We also used the stepwise Cox proportional hazard model to estimate the risk of epilepsy associated with NSDs. The parameters of sex, age, each comorbidity, and drug use (no/yes) were selected stepwise.

In addition, we conducted a Kaplan–Meier analysis on the cumulative incidence of epilepsy in the 2 cohorts by using R software (R Foundation for Statistical Computing, Vienna, Austria) and estimated the difference between the 2 cumulative incidence curves by using a log-rank test.

3. Results

The baseline characteristics of demographic factors in the NSD and comparison cohorts are presented in Table 1. We enrolled 63,865 patients in the NSD cohort and 127,728 patients in the comparison cohort. The distributions of sex and age were similar in the 2 cohorts, with female being the predominant sex (63.7%). Moreover, young to middle-

Table 1
Demographics, comorbidities, and history of drug use in the NSD and comparison cohorts.

	Comparison cohort (N = 127,728)		NSD cohort (N = 63,865)		*P* value
	n	%	n	%	
Sex					0.99
Female	81,390	63.7	40,695	63.7	
Male	46,338	36.3	23,170	36.3	
Age, year					0.99
20–45	53,742	42.1	26,871	42.1	
45–65	47,354	37.1	23,677	37.1	
≥65	26,632	20.9	13,317	20.9	
Mean (standard deviation)[a]	49.8 (16.2)		49.8 (16.2)		0.45
Comorbidity					
Hypertension	47,515	37.2	30,926	48.4	<0.0001
Hyperlipidemia	30,805	24.1	22,565	35.3	<0.0001
Diabetes	23,812	18.6	15,156	23.7	<0.0001
Stroke	17,273	13.5	13,346	20.9	<0.0001
Anxiety	10,749	8.42	23,916	37.4	<0.0001
Depression	4394	3.44	13,716	21.5	<0.0001
Head injury	7945	6.22	5978	9.36	<0.0001
Brain tumors	523	0.41	423	0.66	<0.0001
Drug use					
Non	31,458	24.6	2079	3.26	<0.0001
Zolpidem	1005	0.79	406	0.64	
BZD	77,617	60.8	21,292	33.3	
Both	17,648	13.8	40,088	62.8	
Mean follow-up years (standard deviation)[a]	9.00 (2.44)		9.17 (2.25)		<0.0001

NSD: nonapnea sleep disorder; BZD: benzodiazepine; chi-square test.
[a] Student *t*-test.