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Short communication

Incidence and risk of seizures in Alzheimer's disease: A nationwide population-based cohort study

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ABSTRACT

The reported incidence and risk factors mediating seizures in Alzheimer's disease (AD) have been extremely inconsistent and relevant data is lacking in Asia. We investigated the incidence rate and risk of seizures in AD and in a large, nationwide cohort from Han Chinese. A retrospective population-based study was conducted on the data from Taiwan's National Health Insurance Research Database from 2000 to 2010. To reduce selection bias, we applied propensity scores, wherein 981 patients with AD were matched to 3835 non-AD controls from a pool of 1000,000 randomly sampled cohort dataset. This approach was based on age, sex, comorbidities and previous brain conditions. Incidence rate, cumulative incidence and hazard ratios (HRs) were estimated. During the 10-year follow-up period (mean follow-up time, 4.02 years), 44 out of 937 AD patients (4.7%) developed seizures. The incidence rate in the AD cohort (11.9 per 1000 person-years) was higher than that in the matched cohort (5.7 per 1000 person-years), with an adjusted HR of 1.85 (95% confidence interval [CI], 1.20–2.83, $p = 0.005$). The mean duration from the diagnosis of AD to the occurrence of seizure is 3.6 years. The Cox regression analysis revealed that AD itself is a significant predictor after adjustment for confounders (HR = 2.01, 95% CI, 1.40–2.90, $p < 0.001$). Moreover, age is an independent predictor, with an adjusted HR of 1.03 (95% CI, 1.00–1.05, $p = 0.019$). In conclusion, seizure occurrence in AD is more common than in the matched cohort. Notably, advanced age carries a higher risk for development of seizures in patients with AD.

Introduction

The possible association of epileptic activity to Alzheimer's disease (AD) has been reported by means of animal and clinical studies (Palop and Mucke, 2009; Pandis and Scarmeas, 2012). From the clinical perspective, it has been shown that the incidence of unprovoked seizures in patients with AD is 6 to 10 times more common than age-matched healthy adults (Hauser et al., 1986; Hesdorffer et al., 1996; Hommet et al., 2008). In patients with AD, the reported incidence of seizures during the course of illness varies widely between studies, ranging from 5% to 64% (Larner, 2010; Pandis and Scarmeas, 2012). These conflicting results impede us to draw a precise profile regarding the relationship between AD and unprovoked seizures. Furthermore, the epidemiological data from the Asian population is still lacking.

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It is also scientifically and clinically important to understand the risk factors of new-onset seizures during the AD course. Advanced stage of disease and younger diagnostic age of AD have been thought to be the two most consistent risk factors for developing seizures, although African-American ethnic background, greater cognitive impairment at baseline, antipsychotic use at baseline, diabetes and hypertension have been infrequently and inconsistently reported (Friedman et al., 2012; Pandis and Scarmeas, 2012; Scarmeas et al., 2009). To reconcile the discrepancies among previous studies, we conducted a large-scale, nationwide, retrospective cohort study to evaluate the incidence and predictors of seizures in AD.

Material and methods

Data source

In this population-based retrospective cohort study, we obtained data from Taiwan's National Health Insurance Research Database (NHIRD), which contained all the original claims data of 1 million beneficiaries randomly sampled from 25.68 million individuals in the registry (Lai et al., 2011).

Study design and study population

From January 1, 2000 to December 31, 2010, patients diagnosed with AD and receiving prescriptions of at least one of acetylcholinesterase inhibitors (AChEIs) were identified from the NHIRD. The diagnosis of AD and seizure was described in a greater detail in the Supplementary materials. The main outcomes of the study included the new occurrence of seizure before the end of 2010. The onset of seizure after the diagnosis of AD was defined as the date when the diagnostic code for seizure was noted for the first time in the records.

To minimize potential differences between patients with AD and control subjects, we conducted a 1:4 propensity score-matching algorithm to match each subject in the AD group to a subject from the pool of potential control subjects. The flow chart of patient selection and the method of propensity score were displayed in the Supplementary materials.

Statistical analysis

The two cohorts were followed until the development of seizures, death, or the end of the study period (2010). Pearson χ^2 tests were carried out for categorical variables. The Kaplan–Meier method was employed for estimation of cumulative incidence of seizure in AD group and control group. In the group of people with AD, the multivariate Cox proportional hazards models were used to compute the hazard ratios (HRs) and accompanying 95% confidence intervals (CIs) after adjustment for confounders, and to identify risk factors for seizure. Since head injury and stroke (occurred after AD diagnosis and before endpoint) are important causes of seizure, we calculated head injury and stroke as time-dependent covariates in Cox regression model. Extraction and computation of data were performed using the Perl programming language (version 5.12.2). Microsoft SQL Server 2005 (Microsoft Corp., Redmond, WA, USA) was used for data linkage, processing, and sampling. All statistical analyses were performed using IBM SPSS statistical software or STATA statistical software. p values of <0.05 were considered to be statistically significant.

Results

Characteristics of the study population

A total of 981 diagnosed AD patients and 3835 propensity score-matching controls were identified from the 1000,000 randomly sampled cohort dataset of the Taiwan NHIRD from January 1, 2000 to December 31, 2010. Patients with AD were predominantly female and the mean age was 75.3 years old (standard deviation, SD = 8.2). The comparisons of the demographic characteristics and comorbidities between patients with AD and the matched cohort were listed in the Supplementary materials (Supplementary Table 1).

Comparisons of the seizure incidence between AD and non-AD cases

A total of 131 cases of new seizure events occurred during the follow-up period (Table 1). The overall incidence rate of seizures was found to be 7.0 per 1000 person-years. The seizure incidence in the AD cohorts (11.9 per 1000 person-years) was higher than that in the matched cohorts (5.7 per 1000 person-years, adjusted HR 1.58,

Table 1
Sensitivity analysis of Cox's regression model for risk of seizure in patients with AD and the matched cohorts.

Presence of seizure	Yes/no	Incidence rate (per 10^3 person-years)	Primary analysis			Primary analysis + anti-epileptic drugs[a]		
			Crude HR (95% CI)	Adjusted[b] HR(95% CI)	p Value	Crude HR (95% CI)	Adjusted[b] HR(95% CI)	p Value
Primary analysis[c]								
All patients	131/4554	7.0						
Patients with AD	44/893	11.9	1.59 (1.10–2.29)	1.58 (1.09–2.28)	0.016	1.82 (1.19–2.79)	1.85 (1.20–2.83)	0.005
Matched cohorts	87/3661	5.7	As reference	As reference		As reference	As reference	
Excluding patients who were diagnosed as AD at the last year of the study[c]								
All patients	93/4542	4.9						
Patients with AD	35/892	9.5	1.57 (1.09–2.27)	1.56 (1.08–2.26)	0.018	1.81 (1.18–2.77)	1.83 (1.19–2.81)	0.006
Matched cohorts	58/3650	3.8	As reference	As reference		As reference	As reference	

AD, Alzheimer's disease; HR, hazard ratio; CI, confidence interval.

[a] The diagnosis of seizure were further validated by prescription of at least one of anti-epileptic drugs.

[b] Adjusted for age, sex, and all comorbidities listed in Supplementary Table 1.

[c] Head injury and stroke were calculated as discrete time-varying covariates.