Original Article

Traumatic Brain Injury and the Risk of Incident Dementia in Taiwan: A Population-Based Retrospective Cohort Study Using National Health Insurance Research Database

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Objective: Traumatic brain injury (TBI) has been associated with an increased risk of dementia. The purpose of this retrospective cohort study was designed to investigate the traumatic brain injury and other medical and environmental risk factors associated with dementia.

Patients and methods: Taiwan's National Health Insurance Research Database(NHIRD) was used. We included 7,497 patients received a diagnosis of dementia. Medical disorders and environmental risk factors in 387 patients with Alzheimer's disease (AD) were compared with 7,110 patients with non-AD dementias.

Results: The AD group had a lower prevalence of cerebrovascular diseases (42.64% vs 49.13%; $p = 0.0128$) and respiratory disease (24.29% vs 30.07%; $p = 0.0154$). In multivariate analysis, the risk for AD was increased in patients with cerebrovascular diseases (Adjusted HR, 1.56; 95% CI, 1.33 – 1.82) and respiratory disease (Adjusted HR, 1.20; 95% CI, 1.01 – 1.42).

Conclusions: In a clinical sample of NHIRD, patients with AD don't have a significantly higher risk of TBI after adjustments for selective confounding factors compared with non-AD dementia. Care must be taken in extrapolating from these results because this study was limited by lack of information regarding lifestyles, TBI severity, and methods used in treatments.

Key words: traumatic brain injury, dementia, epidemiology

Introduction

Traumatic brain injury (TBI) occurs when an external force injures the brain. There is a bi-modal peak in the incidence of TBI, with the first peak occurring in young adults, ages 15 to 24. The second peak affects the aging population, occurring after age 75.[1,2] Owing to the increasing use of motor vehicles in developing countries, the incidence of TBI is rapidly growing. Disabilities caused by TBI are a major health and socioeconomic problem.[1-4] These observations suggest that TBIs

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result in major health and socioeconomic problems throughout the world. Indeed, the World Health Organization has reported that traffic accidents are the third highest contributor to the global burden of disease and injury.[1,2] Alzheimer's disease (AD) have been frequently reported to develop in patients with TBI. TBI may adversely affect multiple organ systems and accelerate the progression of AD.[4-8] The mechanisms including accumulation of amyloid β (Aβ) deposits were believed that TBI may influence the incidence of AD. Recently, some prospective longitudinal cohort study found associations between TBI and dementia. However, this finding could not be confirmed in other studies.[9-11] Therefore, there is no conclusive evidence to suggest a relationship between TBI and the risk of AD.

In addition, TBI is known to induce a complex array of inflammatory responses in the acute post-injury phase.[3] Several abnormal proteins aggregation, misfolding or accumulation were found in the TBI brain. The field is lacking a systematic analysis of multiple pathologies in individual cases in a large TBI and control population. The purpose of this population-based cohort study was to determine which type of dementia is associated with TBI in Taiwan.

Methods

Database

This retrospective, population-based cohort study used data sourced from Taiwan's National Health Institute Research Database (NHIRD), which has been described previously.[4, 12] As of 2007, 98.4% of Taiwan's population (approximately 22.96 million) was enrolled. The Longitudinal Health Insurance Database (LHID 2000) randomly selected 1 million insured subjects from the NHIRD database comprising healthcare data from the medical records of all beneficiaries. The data represent original medical claims for all islanders covered by the NHI program and are distributed by sex, age, or amount of average payroll-related insurance payments. Diagnoses and procedures are coded according to the International Classification of Diseases, Clinical Modification, Ninth Edition (ICD-9-CM) code. Insurance reimbursement claims data used in this study were available from NHIRD for public access, and patient identification has been encoded to ensure confidentiality. The details of database generation, monitoring, and maintenance are published online by the Taiwan National Health Research Institutes (TNHRI) (http://nhird.nhri.org.tw). The study was approved by the NHRI Ethics Review Committee, Taiwan.

Study sample

In this retrospective cohort study, we first included patients with at least three NHI ambulatory-claim records, or one inpatient record, in the LHID 2000 and who had a diagnosis of dementia [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 290.0 (senile dementia, uncomplicated); 290.1 (presenile dementia); 290.2 (senile dementia with delusional or depressive features); 290.3 (senile dementia with delirium); 290.4 (arteriosclerotic dementia); 294.1 (dementia in conditions classified elsewhere); 331.0 (AD); 331.1 (Pick disease); and 331.2 (senile degeneration of the brain)] and were treated between January 1, 2002 and December 31, 2007.[4, 12] The study flow chart is shown in Figure 1. We excluded patients who were younger than 20 years of age. In addition, patients who had prior to the index use of health care facilities were identified and excluded from the study. A total of 7497 subjects with dementia from 2002 to 2007 were enrolled in this study.

Main outcome measures

The primary endpoint of this study was to identify comorbidities before the occur-

rence of dementia. The dementia subtypes were AD (ICD-9-CM code 331.0), and non-AD (ICD-9-CM codes 290.0 to 290.4, 294.1, and 331.1 to 331.2). Comorbidities were classified as conditions existing prior to the index day and included diabetes mellitus, dyslipidemia, hypertension, coronary heart disease, heart failure, atrial fibrillation, peripheral vascular disease, cerebrovascular disease, respiratory system, peptic ulcer disease, chronic liver disease, chronic kidney disease, rheumatologic disease, cancer, and TBI. Follow-up data were available for a minimum of 5 years for all subjects.

Statistical analysis

For NHI database analysis, the baseline characteristics of the AD and non-AD groups were compared using Pearson's chi-square test. Selected comorbidities were included only if they occurred in either the inpatient setting or 3 or more ambulatory care claims recorded 1 year before the index ambulatory care visit. Multivariate Cox proportional hazard regression models were conducted to assess the hazard ratios (HR) with 95% confidence intervals (CI) for risk of dementia, adjusting for age, sex, and selected comorbidities. A p value < 0.05 was used to assess statistical significance in this study. The SAS system (SAS System for Windows, version 9.2, SAS Institute, Inc., Cary, NC, USA) was used to perform the statistical analyses.

Results

We included 387 and 7,110 patients in the AD and non-AD cohorts, respectively. No significant differences in age or sex were observed between the groups. Demographic

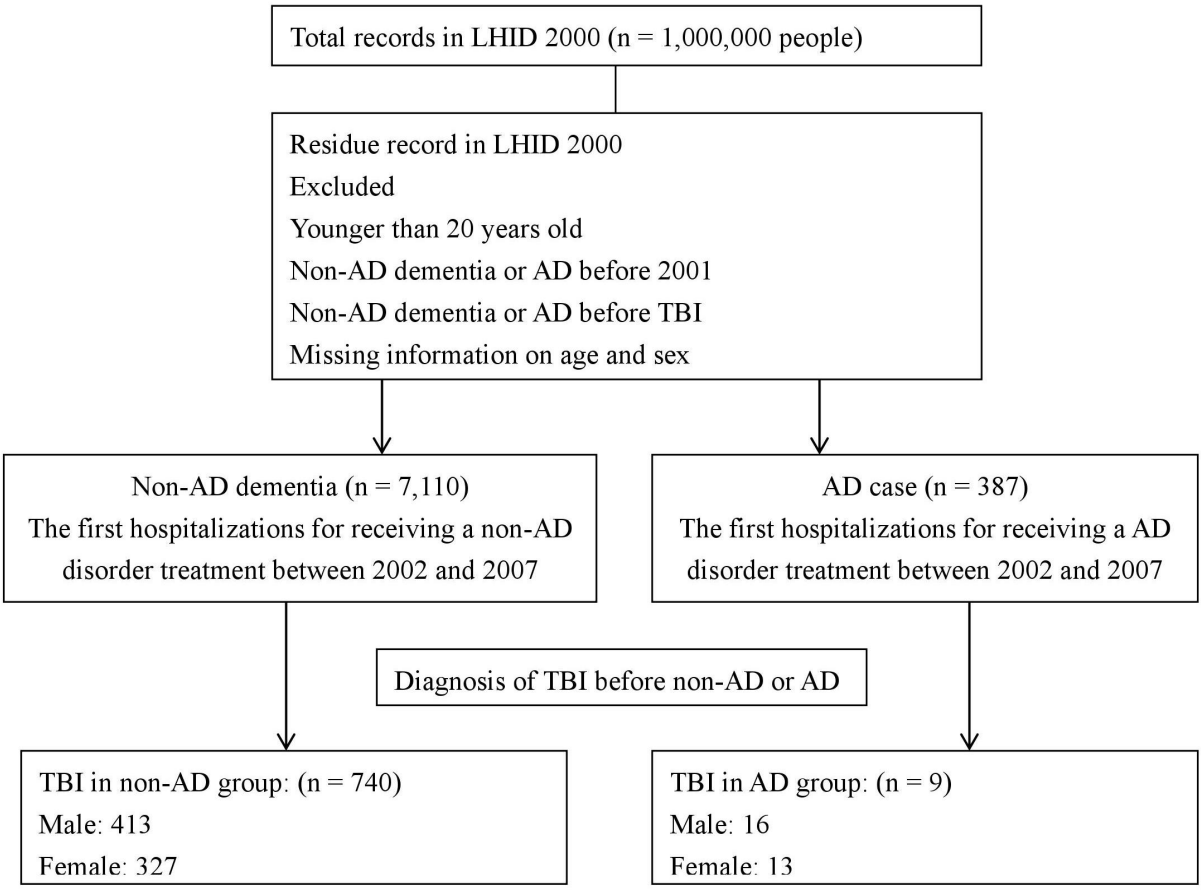

Fig. 1 Flow chart of the study population.

characteristics and comorbidities of the AD and non-AD patients are shown in Table 1. The proportion of women was higher than that of men in both cohorts. The comorbidities of cerebrovascular disease, and respiratory system were more prevalent in the non-AD cohort compared with the AD cohort. Figure 1 is flow chart of the study population.

In Table 2, we performed univariate analyses to predict the risk in patients with dementia. The results demonstrated that patients who had cerebrovascular disease, and respiratory disease were at a higher risk of developing dementia. After including controls for comorbidities, the Cox multivariate proportional hazards analysis showed that cerebrovascular disease (adjusted HR [aHR] = 1.56, 95% confideZnce interval [CI] = 1.33 – 1.82, $p < 0.001$), and respiratory disease (aHR = 1.20, 95% CI = 1.01 – 1.42, p =0.037) were associated with a significantly higher risk of dementia.

In Table 3, We analyzed the HR values based on the gender and age after adjusting the data for the presence of the comorbidities. The HR values obtained within the male group and female group were 0.781 (95%CI 0.459 – 1.329), and 0.701 (95% CI 0.394 – 1.247), respectively.

Table 4 presents HR for association of medical and environmental factors with dementia according to different age groups. Stratified Cox proportional hazard regressions yielded the following results: in the age group of 20 – 39 years, the HR of patients with AD

Table1. Characteristics of the study subjects.

	Patients with AD (n = 387)		Patients with non-AD (n = 7,110)		*p*
Characteristic	n	%	n	%	
Gender					0.3356
Male	176	45.48	3,412	47.99	
Female	211	54.52	3,698	52.01	
Age, mean ± SD	75.2145 ± 11.3810		75.1859 ± 10.8767		0.9600
Age Group					0.1940
20-39	6	1.55	74	1.04	
40-59	31	8.01	500	7.03	
60-74	106	27.39	2,289	32.19	
≥ 75	244	63.05	4,247	59.73	
Geographic region					0.0013
Northern	193	49.87	2,913	40.97	
Central	72	18.60	1,876	26.39	
Southern	113	29.20	2,068	29.09	
Eastern	9	2.33	226	3.18	
Missing	0	0.00	27	0.38	
Comorbidities					
Diabetes	111	28.68	2,332	32.80	0.0924
Dyslipidemia	1	0.26	15	0.21	0.8439
Hypertension	255	65.89	4,989	70.17	0.0739
Coronary Heart Disease	121	31.27	2,444	34.37	0.2095
Heart Failure	56	14.47	946	13.31	0.5119
Atrial Fibrillation	23	5.94	389	5.47	0.6915
Peripheral Vascular Disease	45	11.63	717	10.08	0.3278
Cerebrovascular Disease	165	42.64	3,493	49.13	0.0128*
Respiratory Disease	94	24.29	2,138	30.07	0.0154*
Peptic Ulcer Disease	126	32.56	2,508	35.27	0.2757
Chronic Liver Disease	68	17.57	1,253	17.62	0.9791
Chronic Kidney Disease	60	15.50	1,080	15.19	0.8670
Rheumatologic Disease	11	2.84	322	4.53	0.1168
Cancer	35	9.04	672	9.45	0.7893
TBI	29	7.49	740	10.41	0.0657

Chi-square test and t test

was 0.725 (95% CI, 0.079 – 6.657), in comparison with the non-AD patients; in the age group of 40 – 59 years, the HR of AD patients was 0.802 (95% CI, 0.273 – 2.354); in the age group of 65 – 74 years, the HR of AD patients was 0.895 (95% CI, 0.446 – 1.797). The HR for TBI patients older than 75 years was 0.580 (95% CI,0.341 – 0.987). Furthermore, we found that the adjusted HR in AD patients aged 20–39 years was 0.662 (95% CI, 0.042 – 10.419); in AD patients aged 40-59 years was 0.972 (95% CI, 0.312 – 3.026); the corresponding value in TBI patients aged 65 – 74 years was 0.978 (95% CI, 0.482 – 1.983); and in patients older than 75 years, the HR values for TBI patients were 0.615 (95% CI, 0.360 – 1.051).

Discussion

Concerns about the relationship between

Table2. Prediction for occurrence of dementia

	Crude HR		Adjusted HR	
	OR (95% C.I.)	*p*	OR (95% C.I.)	*p*
AD (vs. non-AD)	0.71 (0.48 – 1.05)	0.083	0.73 (0.50 – 1.08)	0.116
Comorbidities				
Diabetes	1.01 (0.86 – 1.19)	0.894	1.02 (0.87 – 1.20)	0.809
Dyslipidemia	1.26 (0.28 – 5.57)	0.764	1.17 (0.26 – 5.21)	0.836
Hypertension	0.86 (0.73 – 1.02)	0.092	0.88 (0.74 – 1.05)	0.158
Coronary Heart Disease	0.90 (0.76 – 1.06)	0.188	0.86 (0.72 – 1.02)	0.089
Heart Failure	0.86 (0.73 – 1.07)	0.146	0.83 (0.71 – 1.02)	0.063
Atrial Fibrillation	1.03 (0.74 – 1.43)	0.860	1.03 (0.73 – 1.44)	0.872
Peripheral Vascular Disease	0.95 (0.78 – 1.35)	0.090	0.96 (0.79 – 1.42)	0.079
Cerebrovascular Disease	1.59 (1.36 – 1.86)	< 0.001*	1.56 (1.33 – 1.82)	< 0.001*
Respiratory System	1.46 (1.25 – 1.70)	< 0.001*	1.20(1.01 – 1.42)	0.037*
Peptic Ulcer Disease	0.79 (0.66 – 1.16)	0.387	0.80 (0.62 – 1.12)	0.169
Chronic Liver Disease	1.23 (0.74 – 1.72)	0.852	1.25 (0.78 – 1.84)	0.835
Chronic Kidney Disease	0.87 (0.56 – 1.16)	0.284	0.82 (0.72 – 1.22)	0.179
Rheumatologic Disease	0.89 (0.76 – 1.06)	0.188	0.86 (0.72 – 1.02)	0.089
Cancer	1.03 (0.74 – 1.42)	0.860	1.03 (0.73 – 1.44)	0.872
TBI	1.23(1.05 – 1.42)	0.008*	0.98(0.84 – 1.16)	0.848

Table3. Crude and adjusted HRs for association of medical and environmental factors with dementia in each gender group during a 5-year follow-up period from indexed healthcare utilization.

	Patients with AD n = 387		Patients with non-AD n = 7,110		*p*
TBI evet	n	%	n	%	
Total	29	7.49	740	10.41	0.0657
Crude OR (95% CI)	0.698 (0.474 – 1.026)		1		0.0677
Adjusted OR (95% CI)	0.732 (0.496 – 1.080)		1		0.1156
Male	16	9.09	413	12.10	0.2295
Crude OR (95% CI)	0.726 (0.430 – 1.227)		1		0.2320
Adjusted OR (95% CI)	0.781 (0.459 – 1.329)		1		0.3627
Female	13	6.16	327	8.84	0.1788
Crude OR (95% CI)	0.677 (0.382 – 1.200)		1		0.1815
Adjusted OR (95% CI)	0.701 (0.394 – 1.247)		1		0.2266

TBI and dementia have long existed. However, dementia is not a single disease; it's an overall term — like heart disease — that covers a wide range of specific medical conditions, including AD. AD is the most common form of dementia. When we analyzed a distinct medical and environmental profile for AD versus non-AD dementias in this sample, we found that AD was not the most common form of post TBI dementia. Further multivariate stratified analysis showed that the risk of dementia in patients with AD was higher in subgroups, including cerebrovascular disease and respiratory disease.

In rodent models, a common factor between TBI and dementia is the abnormal aggregation, accumulation, and/or disposition of proteins in the brain. Amyloid-β-related neurodegenerative pathophysiologic processes could help explain the link between TBI and AD.[13, 14] Amyloid precursor protein is upregulated immediately after TBI and β-amyloid despoists over weeks and months. β-secretase, and presenilin-1, a γ-secretase complex protein, also accumulate after injury. Amyloid precursor protein, β-amyloid precursor protein-cleaving enzyme-1, and presenilin-1 serve as sources of amyloid-β peptide deposition after TBI. These findings have led to the hypothesis that β-amyloid peptide and tau accumulation are important mechanisms in the long-term neurodegenerative effects of TBI.

However, human pathologic studies addressing the mechanisms of post-TBI dementia are limited. Recent studies in humans have indicated a positive correlation between changes in brain interstitial fluid (ISF) amyloid β concentrations and neurological status. β-amyloid accumulation is rapid and can be detected in tissue excised surgically within hours of injury.[13-20] Then diffuse β-amyloid plaques are found in up to 30% of patients who die acutely following TBI. and support the hypothesis that AD is the most common form of dementia.

The mechanisms underlying the association of TBI and the incidence of dementia are exceedingly complex.[22,24] In fact, in TBI, multiple pathologies, including a distinctive pattern of progressive brain atrophy and accumulation of hyperphosphorylated tau neurofibrillary and glial tangles, dystrophic neurites, 43 kDa TAR DNA-binding protein (TDP-43) neuronal and glial aggregates, microvascu-

Table4. Crude and adjusted HRs for association of medical and environmental factors with dementia in different age groups during 5-year follow-up period from index healthcare utilization.

	Patients with AD n = 387		Patients with non-AD n = 7,110		*p*
TBI evet	n	%	n	%	
20 – 39	1	0.26	16	0.23	0.7754
Crude OR (95% CI)	0.725 (0.079 – 6.657)		1		0.7763
Adjusted OR (95% CI)	0.662 (0.042 – 10.419)		1		0.7691
40 – 59	4	1.03	78	1.09	0.6868
Crude OR (95% CI)	0.802 (0.273 – 2.354)		1		0.6875
Adjusted OR (95% CI)	0.972 (0.312 – 3.026)		1		0.9606
60 – 75	9	2.33	215	3.02	0.7551
Crude OR (95% CI)	0.895 (0.446 – 1.797)		1		0.7553
Adjusted OR (95% CI)	0.978 (0.482 – 1.983)		1		0.9503
> 75	15	2.44	431	6.06	0.0422
Crude OR (95% CI)	0.580 (0.341 – 0.987)		1		0.0446
Adjusted OR (95% CI)	0.615 (0.360 – 1.051)		1		0.0753

lopathy, myelinated axonopathy, neuroinflammation, and white matter degeneration, occur simultaneously. However, systematic analyses of multiple pathologies in individual cases in a large TBI and control population have not been conducted.[9-13] Therefore, the most common dementia post TBI is hard to know.

The main strength of our study is its large sample, and the problems of insufficient power and the effect of selection biases were minimized. Second, a retrospective cohort was used in our study; this provides more evidence than case-control or cross-sectional designs.

There are several limitations of this study. First, the diagnoses of dementia were made with at least 3 NHI ambulatory-claim records, or 1 inpatient record, in the LHID 2000. The prevalence of TBI might underestimate due to cases in which patients with very minor. However, the prevalence rate of AD was low in this study, which could be due to a relatively young elderly population and a high mortality from dementia in Taiwan. The incidences are likely to vary based on the study design. Some approaches, using Aricept, Exelon, Reminyl and Memantine to identify AD, can lead to lower estimates. Other methods that are less restrictive may lead to higher estimates. In the current study, cases were only included if they sought treatment and were diagnosed with AD. Therefore, individuals who were not diagnosed, or who were misdiagnosed, would not have been included.

Second, the NHI database includes only patients who sought treatment for TBI and dementia. Some information was not available, such as low educational attainment, lifestyle, severity of TBI, and laboratory examinations. Therefore, these variables could not be adjusted for in the analysis. Finally, information on causes of deaths could not be obtained from the NHI database, thereby making an analysis of the mortality ratio related to TBI impossible.

Conclusion

From the results of this nationwide retrospective cohort study, patients with AD don't have a significantly higher risk of TBI after adjustments for selective confounding factors compared with non-AD dementia. Although the evidence suggested that TBI was a risk factor for dementia, there is limited information on the type, frequency, or amount of trauma that was necessary to induce the neurodegenerative processes. The underlying pathology of this association have been difficult to establish. Care must be taken in extrapolating from these results, and further investigation in this area is needed to detect the mechanisms for such effects.

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