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ARTICLE

Spinal cord injury and Alzheimer's disease risk: a population-based, retrospective cohort study

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Abstract

Study design Propensity score-matched, retrospective cohort study.

Objectives To determine the risk of developing Alzheimer's disease (AD) in patients with spinal cord injury (SCI).

Setting The present study used Taiwan's National Health Insurance Research Database.

Methods A total of 9257 patients who had ⩾2 ambulatory visits with a diagnosis of SCI in 2001 were included in the SCI group. The non-SCI group consisted of 37,028 propensity score-matched patients without a diagnosis of SCI. The cumulative incidence of AD was estimated for each of the two patient groups using the Kaplan–Meier method. Stratified Cox proportional hazard regression was then employed to assess the influence of SCI on the risk of AD.

Results During the follow-up period, 25 subjects in the SCI group and 57 in the non-SCI group developed AD. The cumulative incidence of AD in the SCI group was higher than in the non-SCI group ($P = 0.0168$); and the hazard ratio of AD for the SCI group, as compared to the non-SCI group, was 1.71 (95% CI 1.06–2.76, $P = 0.0273$).

Conclusions This study suggests that patients with SCI have an increased risk of developing AD.

Introduction

Alzheimer's disease (AD), one of the most common neurodegenerative disorders, is characterized by progressive cognitive decline and, eventually, complete functional dependence, causing enormous medical and socioeconomic burdens [1]. The main neuropathological features of AD are extracellular neuritic plaques consisting of beta-amyloid, and intracellular neurofibrillary tangles composed of tau protein. These pathological changes tend to spread gradually throughout the brain as AD progresses [2]. Traumatic brain injury (TBI) has been associated with an increased risk of developing post-traumatic neurodegeneration and chronic traumatic encephalopathy [3, 4]. Spinal cord injury (SCI) is another central nervous system (CNS) injury that can lead to neuronal damage, inflammation, and neurodegeneration [3, 5]. Deposition within the spinal cord of amyloid precursor protein (APP), the precursor of beta-amyloid, has been observed in patients with SCI [6–8]. However, epidemiological data on the association between SCI and AD remain sparse and controversial [9]. Accordingly, we performed this large-scale population-based cohort study to evaluate the risk of AD among patients with SCI in a nationwide population sample.

Methods

Data source

The data used in this study were obtained from Taiwan's National Health Insurance (NHI) Research Database for the

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years 2000 through 2003. This data has also been used in our previous studies on the association between SCI and neurodegenerative disorders [10, 11]. The NHI is a compulsory single-payer healthcare system, covering more than 97% of the country's population. To ensure compliance with the personal privacy regulations in Taiwan, individual data was kept confidential and all personal identification numbers were encrypted before data processing. Because the data were analyzed in a pseudonymized manner for academic research, the present study was exempted from full review by the Research Ethics Committee of the National Taiwan University Hospital, and the individual consent was waived.

Study subjects and design

We used a retrospective cohort study design to investigate the association between SCI and the risk of AD. Propensity-score matching was used to generate two comparable groups of patients, one with and one without SCI, thus minimizing the potential for confounding effects to arise due to imbalances in the baseline characteristics [11, 12]. The advantage of the propensity score matching is that it enables us to investigate the risk of a rare outcome (AD) in SCI patients by simultaneously controlling for many potential confounders. Such study design has also been used in several our previous studies [10, 11, 13].

The SCI group consisted of patients from the NHI database who were aged between 40 and 90, and who had a diagnosis of SCI (ICD-9-CM codes 806 or 952) during ambulatory medical-care visits in calendar year 2001. To increase the likelihood that such diagnoses were accurate, only patients who had two or more ambulatory visits in which a diagnosis of SCI was recorded within this 1-year period were included ($n = 9321$). The first such visit was defined as the index visit. Those who had been diagnosed with AD (ICD-9-CM codes 331.0) prior to the index visit ($n = 22$) were excluded, leaving a total of 9299 patients in the SCI group at this stage.

All of the SCI group's outpatient and inpatient records in the NHI database from the 12-month period before the index visit were checked for information about pre-existing comorbidities, including diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), gout (ICD-9-CM code 274), coronary heart disease (ICD-9-CM codes 410–414), atrial fibrillation (ICD-9-CM code 427.31), rheumatic heart disease (ICD-9-CM codes 393–398), stroke (ICD-9-CM codes 430–438), TBI (ICD-9-CM codes 801–804, 850–854), and chronic kidney disease (ICD-9-CM codes 580–587). A particular comorbid condition was deemed present if the patient had ⩾1 hospital discharge or ⩾2 ambulatory visits with the relevant diagnosis code. Socioeconomic variables, including monthly income, geographic region of residence, and place of residence's level of urbanization, were also used as matching variables because previous studies have shown their impact on the risk of AD [14]. As an indicator of monthly income, we categorized the NHI's insured payroll-related amounts into four levels (i.e., NT$0, NT$1-15840, NT$15841-25000, and ⩾NT$25001). The first cut-off point of NT$15840 was selected because it was the government-designated minimum monthly salary for full-time employees. The seven-level typology of urbanization in Taiwan devised by the National Health Research Institutes [15] was simplified into a five-level version, with level 1 being "most urbanized", and level 5 (a combination of the original levels 5, 6, and 7) "least urbanized". The geographic region of each subject's residence was classified as Northern, Central, Eastern, or Southern Taiwan. Of the 9299 individuals in the SCI group, 42 were excluded as the information of the geographic location of residence was missing from Taiwan's household registry, leaving 9257 subjects in the final SCI group.

The non-SCI group was selected from among the remaining patients in the NHI database. For this group, the index visit was defined as the first ambulatory visit in 2001, and only patients who had at least two ambulatory visits in 2001 were included. The exclusion criteria were (1) a diagnosis of SCI (ICD-9-CM codes 806 and 952) prior to the index visit and/or (2) a diagnosis of AD (ICD-9-CM code 331.0) prior to the index visit. Information about comorbid conditions and socioeconomic variables were obtained in the same manner as for the SCI group.

This study used a two-stage approach to carry out propensity-score matching, as described in our previous works [10, 11]. In the first stage, we randomly sampled up to 60 age- and sex-matched non-SCI individuals who meet the above inclusion and exclusion criteria for each patient in the SCI group, yielding a total of 555,390 non-SCI individuals. In the second stage, we fit a logistic regression model that included covariates of age, sex, comorbid conditions, and socioeconomic factors to predict the probability (i.e., propensity score) of SCI for each patient. Then, based on these propensity scores, an eight-to-one digit greedy matching algorithm [16] was employed to select 4 matched control subjects for each SCI patient from the non-SCI pool, resulting in a propensity-score-matched non-SCI group of 37,028 individuals.

Outcomes

From the NHI database, we retrieved the records of each subject from his/her index visit through the end of 2003 (hereafter, the "follow-up period"). Each subject was tracked from the index visit until the earliest of (1) his/her first diagnosis of AD (ICD-9-CM code 331.0, as confirmed by

Table 1 Demographic and clinical characteristics for the spinal cord injury (SCI) and non-SCI groups at the first stage of matching, with age and sex matched

Variable	SCI group ($N = 9257$)	Non-SCI group ($N = 555{,}390$)	p value	Standardized difference
Sex (female)	4948 (53.5)	296,850 (53.5)	0.9962	0.0000
Age (years)	63.1 ± 13.1	62.9 ± 13.1	0.1932	0.0136
Diabetes (yes)	1416 (15.3)	71,944 (13.0)	< 0.0001	0.0673
Hypertension (yes)	3082 (33.3)	174,736 (31.5)	0.0002	0.0392
Hyperlipidemia (yes)	763 (8.2)	46,705 (8.4)	0.5658	0.0060
Gout (yes)	560 (6.1)	34,987 (6.3)	0.3259	0.0104
Coronary heart disease (yes)	1141 (12.3)	63,074 (11.4)	0.0036	0.0300
Atrial fibrillation (yes)	106 (1.1)	5244 (0.9)	0.0479	0.0198
Rheumatic heart disease (yes)	81 (0.9)	4157 (0.8)	0.1618	0.0141
Stroke (yes)	1106 (11.9)	42,404 (7.6)	< 0.0001	0.1455
Traumatic brain injury (yes)	749 (8.1)	7245 (1.3)	< 0.0001	0.3250
Chronic kidney disease (yes)	467 (5.0)	18,525 (3.3)	< 0.0001	0.0854
Monthly income			< 0.0001	0.2529
NT$0	3418 (36.9)	172,682 (31.1)		
NT$1-NT$15840	1791 (19.3)	80,395 (14.5)		
NT$15841-NT$25000	3302 (35.7)	223,803 (40.3)		
⩾NT$25001	746 (8.1)	78,510 (14.1)		
Urbanization level			< 0.0001	0.1431
1 (most urbanized)	1585 (17.1)	104,135 (18.7)		
2	1065 (11.5)	60,562 (10.9)		
3	1904 (20.6)	134,739 (24.3)		
4	1927 (20.8)	88,979 (16.0)		
5 (least urbanized)	2776 (30.0)	166,975 (30.1)		
Geographic region			< 0.0001	0.1069
Northern	3565(38.5)	242,111 (43.6)		
Central	1968 (21.2)	103,404 (18.6)		
Southern	3413 (36.9)	193,207 (34.8)		
Eastern	311 (3.4)	16,668 (3.0)		
Propensity score	0.024 ± 0.025	0.016 ± 0.011	< 0.0001	0.3968

Data are expressed as N (%) or the mean ± SD. US $1 = NT $34 in 2001

⩾1 hospital discharge or ⩾2 ambulatory visits); (2) death; or (3) the end of the follow-up period. The primary endpoint of analysis was the date of a given patient's first occurrence of AD within the follow-up period. The study cohort was linked to Taiwan's mortality registry to ascertain the patients died during the follow-up period.

Statistical analysis

We used the χ^2 test and Student's t-test to examine the differences in baseline characteristics between the SCI and non-SCI groups. The covariate balance before and after propensity-score matching was assessed using the standardized-difference method, which is not affected by sample size and is thus preferred over hypothesis-testing methods [17]. An absolute standardized difference of < 0.1 for a given covariate indicates a negligible imbalance. The incidence rate of AD was calculated as the number of AD cases divided by AD-free person-years. Poisson regression was used to estimate the incidence rate ratio of AD between the SCI and non-SCI groups.

The cumulative incidence rate of AD was estimated using the Kaplan–Meier method. Cox proportional-hazards regression stratified by the propensity score matching set was used to estimate the effect of SCI on the subsequent occurrence of AD. An alpha level of 0.05 was considered statistically significant for all analyses, which were performed using SAS 9.4 software (SAS Institute, Cary, NC).

Results

The proportion of SCI patients and controls who had a previous diagnosis of AD before the index visit was 0.24% and 0.14%, respectively. Table 1 presents the socio-economic and clinical characteristics of the SCI and non-SCI groups at the first stage of matching, with age and sex-matched. As compared to the non-SCI group, the SCI group had a higher prevalence of certain comorbid conditions: i.e., diabetes ($P < 0.0001$), hypertension ($P = 0.0002$), coronary heart disease ($P = 0.0036$), atrial fibrillation ($P = 0.0479$), stroke ($P < 0.0001$), TBI ($P < 0.0001$), and chronic kidney disease ($P < 0.0001$). There were also significant differences between the SCI and non-SCI groups in terms of monthly income, geographic region, and urbanization level. Before matching, the absolute standardized differences were >0.1 for stroke, TBI, monthly income, urbanization level, geographic region, and propensity score. After propensity-score matching, as shown in Table 2, the matched groups were well balanced in all baseline characteristics, as indicated by the absolute standardized differences being < 0.1 for all covariates.

The number of AD cases and the hazard ratios (HRs) of AD for the two propensity-score-matched groups are presented in Table 3. Of the 9257 patients with SCI, 25 developed AD during 22044.7 person-years of follow-up, representing an incidence rate of 11.34 (95% confidence interval (CI), 7.34–16.74) per 10,000 person-years. Of the 37,028 subjects in the non-SCI group, 57 developed AD during 88374.0 person-years of follow-up: an incidence rate of 6.45 (95% CI, 4.88–8.36) per 10,000 person-years. The incidence ratio of AD for the SCI group was 1.76 (95% CI, 1.10–2.81, $P = 0.0186$) compared to the non-SCI group. Figure 1 shows the cumulative incidence curves of AD for the two groups. The cumulative incidence of AD during the 3-year follow-up for the SCI group was significantly higher than that for the non-SCI group ($P = 0.0168$), indicating that the SCI group had a higher risk of developing AD. The stratified Cox regression analysis showed that the SCI group's HR of AD was 1.71 (95% CI, 1.06–2.76, $P = 0.0273$) as compared to the non-SCI group.

Sensitivity analysis

To assess whether our primary results are robust to different case definitions, we conducted the following sensitivity analyses. First, since the SCI subjects had a higher prevalence of TBI, which may confound the association between SCI and AD. We performed sensitivity analysis excluding all patients with a previous diagnosis of TBI. The results show that SCI was still associated with a higher risk of AD (HR 1.92, 95% CI, 1.17–3.17, $P = 0.0101$). Furthermore, we excluded all subjects with a previous diagnosis of either TBI or post-concussion syndrome (ICD-9-CM code 310.2) from the analysis. The estimated HR was 1.92 (95% CI, 1.16–3.15, $P = 0.0106$), still suggesting an increased risk of AD in the SCI group. Second, we peformed additonal analysis using dementia (ICD-9-CM codes 290, 294) as the outcome to evaluate the risk of dementia for SCI patients. The results showed that the SCI group had a higher risk of dementia (HR 1.25, 95% CI, 1.12–1.40, $P < 0.0001$) compared to the non-SCI group.

Discussion

This large-scale longitudinal follow-up study showed that SCI patients had a higher risk of developing AD than non-SCI subjects did. A recent study [9] used one-million beneficiaries sampled from the Taiwan's NHI database, and found that there was no statistically significant increase in the AD risk for SCI patients (adjusted HR 1.76, 95% CI 0.69–4.48), but SCI patients had a higher risk of other types of dementia [9]. In the present study, we used the large-scale complete NHI database (more than 22 million beneficiaries), and applied propensity score matching to control for all baseline covariates simultaneously. Our study improved the precision of estimation, and showed that SCI patients were at a higher risk of developing AD (HR 1.71, 95% CI, 1.06–2.76, $P = 0.0273$). Although the exact mechanism(s) by which SCI affects AD risk remains unclear, we can offer the following possible explanations.

First, studies of humans [6–8] and animals [18, 19] have shown that after SCI occurs, APP is deposited throughout the spinal cord, and can persist for a prolonged period – sometimes decades – after the traumatic event [6–8]. Post-SCI accumulation of APP can lead to increased beta-amyloid production in the spinal cord, as has been observed in animal models [18, 19]. Beta-amyloid is not only the key component of neuritic plaques, the histopathological hallmark of AD, but also an active player in the pathogenesis of the disease. Beta-amyloid accumulation, in turn, can lead to excessive oxidative stress, increased inflammation, and mitochondrial dysfunction, resulting in neuronal degeneration and death [20]. Beta-amyloid can be taken up by axons, transported retrogradely to the cell body, and then transmitted to various regions of the brain via neuronal connections [21]. This transmission process may be essential to the progression of AD within the brain [21]. We therefore suggest that increased accumulation of beta-amyloid and APP in the CNS may predispose patients with SCI to a higher risk of AD.

Second, several human [22, 23] and animal [24] studies have found elevated concentrations of tau protein in the cerebrospinal fluid (CSF) after SCI. Tau protein is a key element in AD pathogenesis, and tau accumulation has been

Table 2 Demographic and clinical characteristics for the spinal cord injury (SCI) and non-SCI groups after propensity score matching

Variable	SCI group ($N = 9257$)	Non-SCI group ($N = 37,028$)	Standardized difference
Sex (female)	4948 (53.5)	19,393 (52.4)	0.0216
Age (years)	63.1 ± 13.1	62.8 ± 13.1	0.0263
Diabetes (yes)	1416 (15.3)	5783 (15.6)	0.0089
Hypertension (yes)	3082 (33.3)	12,182 (32.9)	0.0084
Hyperlipidemia (yes)	763 (8.2)	3158 (8.5)	0.0103
Gout (yes)	560 (6.0)	2297 (6.2)	0.0064
Coronary heart disease (yes)	1141 (12.3)	4513 (12.2)	0.0042
Atrial fibrillation (yes)	106 (1.1)	397 (1.1)	0.0070
Rheumatic heart disease (yes)	81 (0.9)	317 (0.9)	0.0020
Stroke (yes)	1106 (11.9)	4520 (12.2)	0.0080
Traumatic brain injury (yes)	749 (8.1)	2978 (8.0)	0.0018
Chronic kidney disease (yes)	467 (5.0)	1942 (5.2)	0.0091
Monthly income			0.0449
NT$0	3418 (36.9)	13,163 (35.6)	
NT$1- NT$15840	1791 (19.3)	7419 (20.0)	
NT$15841- NT$25000	3302 (35.7)	13,083 (35.3)	
⩾NT$25001	746 (8.1)	3363 (9.1)	
Urbanization level			0.0185
1 (most urbanized)	1585 (17.1)	6448 (17.4)	
2	1065 (11.5)	4359 (11.8)	
3	1904 (20.6)	7424 (20.0)	
4	1927 (20.8)	7831 (21.2)	
5 (least urbanized)	2776 (30.0)	10,966 (29.6)	
Geographic region			0.0056
Northern	3565 (38.5)	14,324 (38.7)	
Central	1968 (21.2)	7901 (21.3)	
Southern	3413 (36.9)	13,581 (36.7)	
Eastern	311 (3.4)	1222 (3.3)	
Propensity score	0.024 ± 0.025	0.024 ± 0.025	0.0012

Data are expressed as N (%) or the mean ± SD. US $1 = NT $34 in 2001

Table 3 Number of Alzheimer's disease (AD) cases and the hazard ratio of AD for the matched spinal cord injury (SCI) and non-SCI groups

Variable	SCI group ($N = 9257$)	Non-SCI group ($N = 37,028$)
AD cases, N	25	57
Person-years	22044.7	88374.0
Risk per 10,000 person-year (95% CI)	11.34 (7.34–16.74)	6.45 (4.88–8.36)
Hazard ratio (95% CI)	1.71 (1.06–2.76)*	1.00

*$P = 0.0273$

found to progress in a caudal to rostral direction in AD [2]. While it has been suggested that the transmission of tau follows a prion-like neuron-to-neuron pattern [2, 25, 26], some evidence indicates another possible route for its propagation: through the CSF [25, 26]. In an animal model, tau protein released by damaged neurons was shown to reach the CSF and spread to distant regions; to be taken up by neurons and glia cells [25]; and then to spread further via neuron-to-neuron transmission [26]. The same transmission mechanism for tau may also occur in the human CNS [25]. Tau exerts its toxicity by impairing axonal transport, leading to cytoskeletal collapse and eventually, neuronal dysfunction and death [20]. We therefore speculate that elevated tau concentrations in the CSF after SCI, and the subsequent spread of tau, may also contribute to SCI patients' higher risk of developing AD.

Third, SCI patients exhibit chronic systemic inflammation, as demonstrated by their persistently elevated concentrations of proinflammatory markers such as serum TNF-α [27, 28], IL-6 [27], and C-reactive protein (CRP) [29]. Systemic inflammation can be an important driving

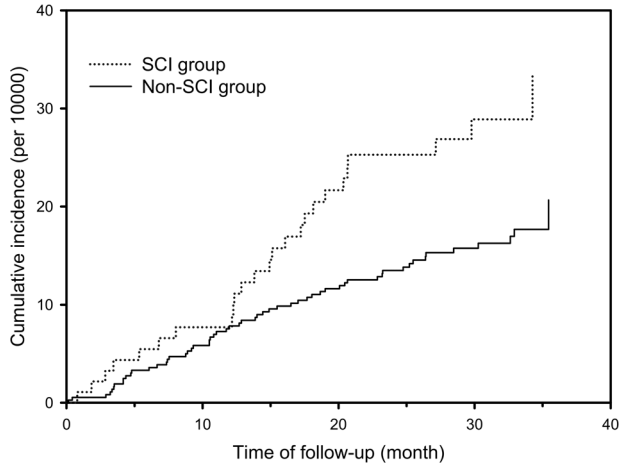

Fig. 1 Cumulative incidence of Alzheimer's disease (AD) for the spinal cord injury (SCI) group (dotted line) and the non-SCI group (solid line)

force for neuroinflammation [30, 31], which in turn plays an important role in the pathogenesis of AD [30–32]. Animal studies have shown that peripheral inflammation exaggerates both CNS inflammation [33, 34] and beta-amyloid deposition [33]; and human studies have demonstrated that elevated levels of IL-6 [35], TNF-α [36], and CRP [35] are associated with an increased risk of AD [35, 36]. We therefore hypothesize that the association between SCI and AD may be mediated by SCI-related systemic inflammation, which by inducing neuroinflammation could lead to a higher risk of AD.

While previous histopathological studies based on animal and human models have suggested neurodegeneration in CNS may occur after SCI, epidemiological evidence for the association between SCI and neurodegenerative disorders is limited. The present cohort study demonstrated a temporal sequence between SCI and AD, which suggests a temporal association between SCI and AD, and provides epidemiological evidence supporting the hypothesis that SCI may contribute to a higher risk of neurodegenerative disorders in CNS. Moreover, in the sensitivity analysis, the positive association between SCI and AD was not attenuated by excluding all subjects with previous diagnosis of TBI or post-concussion syndrome, suggesting that SCI is independently associated with an increased risk of AD.

Nevertheless, several limitations of this research should be noted. First, the diagnoses of SCI, AD, and comorbid conditions were entirely determined using the ICD codes from the NHI database, which may raise concerns about diagnostic accuracy. However, the Bureau of the NHI samples claim data from every hospital in the NHI program, and reviews charts regularly to verify diagnostic validity as well as the quality of care being provided. For these reasons, the NHI database is widely accepted as an appropriate database for biomedical research [11, 13]. Second, due to the inherent limitation of the NHI database, the information about certain lifestyle factors such as smoking, alcohol consumption, physical inactivity, and obesity is lacking, which may influence the interpretation of our results. Third, since the present study used NHI database from 2000 to 2003, the median follow-up time was only 31 months and therefore the long-term effects of SCI on the risk of developing AD cannot be evaluated. And finally, most inhabitants of Taiwan are of Chinese ethnicity, and it is unclear whether the findings from the present study can be generalized to other ethnic populations.

In conclusion, the present longitudinal follow-up study of a nationwide population-based cohort shows that patients with SCI are at an increased risk of developing AD. Further studies are required to elucidate the mechanism(s) that underlie this association.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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