JOURNAL OF NEUROTRAUMA 32:655–659 (May 1, 2015)

DOI: 10.1089/neu.2014.3723

Spinal Cord Injury Is Related to an Increased Risk of Multiple Sclerosis: A Population-Based, Propensity Score-Matched, Longitudinal Follow-Up Study

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Abstract

Multiple sclerosis (MS) is a demyelinating autoimmune disease of the central nervous system (CNS). Trauma to the CNS has been postulated to play a role in triggering CNS autoimmune disease. Although the association between traumatic brain injury and MS has been suggested in previous studies, epidemiological data on the association between spinal cord injury (SCI) and MS is still lacking. The aim of the present population-based, propensity score–matched, longitudinal follow-up study was therefore to investigate whether patients with SCI were at a higher risk of developing MS. A total of 11,913 subjects ages between 20 and 90 years with at least two ambulatory visits with the principal diagnosis of SCI in 2001 were enrolled in the SCI group. We used a logistic regression model that included age, sex, pre-existing co-morbidities, and socioeconomic status as covariates to compute the propensity score. The non-SCI group consisted of 59,565 propensity score–matched, randomly sampled subjects without SCI. Stratified Cox proportional hazard regression with patients matched by propensity score was used to estimate the effect of SCI on the risk of developing subsequent MS. During follow-up, five subjects in the SCI group and four in the non-SCI group developed MS. The incidence rates of MS were 17.60 (95% confidence interval [CI], 5.71-41.0) per 100,000 person-years in the SCI group and 2.82 (95% CI, 0.77-7.22) per 100,000 person-years in the non-SCI group. Compared with the non-SCI group, the hazard ratio of MS for the SCI group was 8.33 (95% CI, 1.99-34.87, $p = 0.0037$). Our study therefore shows that patients with SCI have an increased risk of developing MS.

Key words: multiple sclerosis; propensity score; risk factors; spinal cord injury

Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS).[1,2] Although its cause is not well established, an autoimmune response triggered by environmental factors and genetic susceptibility may play a central role in the pathogenesis of MS.[1,3] Trauma to the CNS, including the brain and spinal cord, has been postulated to be an important triggering factor in MS.[4–6] However, previous studies on the relationship between MS and CNS injury have generated inconsistent results.

Three epidemiologic studies have examined whether there is an association between head injury and MS.[7–9] One population-based cohort study in a Chinese population showed an increased risk of developing MS after head injury,[9] whereas two cohort studies, performed in Denmark[8] and England,[7] failed to demonstrate a positive relationship between head injury and MS. Further, to our knowledge, no research has been conducted on the relationship between spinal cord injury (SCI) and MS. We therefore carried out this population-based, propensity score–matched, longitudinal follow-up study to determine whether patients with SCI are at a higher risk of developing MS.

Methods

Data source

The data used in this study were obtained from the complete National Health Insurance (NHI) claim database in Taiwan for the period 2000 to 2003. The NHI program has been implemented in Taiwan since 1995, and the coverage rate was 96% of the whole population in 2000 and 97% at the end of 2003 (i.e., more than 21.9 million persons). It should be noted that the rationale for using the

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NHI database after 2000 is that from January 1, 2000, according to the rules of the Bureau of NHI, NHI claim data have been encoded using the standardized *International Classification of Disease, 9th Revision, Clinical Modification* (ICD-9-CM). To keep individual information confidential so as to satisfy regulations on personal privacy in Taiwan, all personal identification numbers in the data were encrypted by converting them into scrambled numbers before data processing. This study was exempt from full review by the National Taiwan University Hospital Research Ethics Committee and the need for informed consent was waived because the data used consisted of de-identified secondary data released for research purposes and were analyzed anonymously, thus complying with the regulations of the Department of Health, Executive Yuan, Republic of China.

Study subjects and design

We used a cohort study design to investigate the effect of SCI on the risk of developing MS. The study population consisted of a SCI group and a non-SCI group, both selected from Taiwanese residents in the complete NHI claim database in 2001, in which more than 21.6 million persons were registered. To control for potential confounding effects of an imbalance in measured baseline characteristics, we used propensity score matching to create comparable cohorts of patients with and without SCI.[10,11]

The SCI group consisted of subjects ages 20 to 90 years who had received a diagnosis of SCI (ICD-9-CM codes 806, 952) in ambulatory medical care visits between January 1, 2001, and December 31, 2001. To maximize case ascertainment, only patients who had at least two ambulatory visits with the diagnosis of SCI in this period were initially considered for inclusion in the SCI group ($n = 11{,}976$). The index visit was defined as the first ambulatory visit in 2001 during which a diagnosis of SCI was recorded. Subjects with a previous diagnosis of MS (ICD-9-CM codes 340) before the index visit ($n = 13$) were excluded. A total of 11,963 subjects was enrolled at this stage in the SCI group.

Information about the pre-existing comorbidities of diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401-405), and dyslipidemia (ICD-9-CM code 272) was acquired by tracking all the ambulatory medical care and inpatient records in the NHI database in the year before the index visit. The case ascertainment for these medical comorbidities was defined on the basis of ≥ 1 hospital discharge or ≥ 2 ambulatory visits with a relevant diagnosis code.

Since previous studies have suggested that the risk of MS may be affected by socioeconomic status, such as geographical region,[12,13] level of urbanization,[14] and income level,[15] these factors also were included as variables in assessing the risk of MS. Information about the place of residence of each subject was obtained from the population household registry and the location was classified as Northern, Central, Eastern, or Southern Taiwan. As recommended by the Taiwan National Health Research Institute,[16] urbanization levels in Taiwan were initially classified into seven strata, with level 1 referring to ''most urbanized'' and level 7 to ''least urbanized'' communities; however, since the numbers of subjects in levels 5, 6, and 7 were relatively small, these three levels were merged into a single group labeled level 5.

For information on income level, we used the insured payroll-related amount as a proxy for income, with levels of New Taiwan dollar (NT$)0, NT$1-NT$15,840, NT$15,841-NT$25,000, and ≥ NT$25,001. We selected NT$15840 as the first cutoff point of income level because this is the government-stipulated minimum wage for full-time employees in Taiwan. Since household registry information was not available for 50 of the 11,963 subjects in the SCI group, these 50 subjects were excluded from the analysis, leaving 11,913 subjects in the final SCI group.

The non-SCI group was taken from the remaining subjects without a diagnosis of SCI in the same 2001 NHI claim database. The first ambulatory medical care visit during 2001 was assigned as the index visit. The exclusion criteria for recruiting subjects into the non-SCI group were: 1) a previous diagnosis of SCI (ICD-9-CM codes 806, 952) before the index visit; 2) a previous diagnosis of MS (ICD-9-CM codes 340) before the index visit; and 3) a previous diagnosis of stroke (ICD-9-CM codes 430-438), traumatic brain injury (ICD-9-CM codes 801-804 or 850-854), anterior horn cell disease (ICD-9-CM codes 335), or Alzheimer's disease (ICD-9-CM codes 331.0) before the index visit. Information about pre-existing co-morbidities and socioeconomic status was obtained as described above.

Because the number of subjects in the NHI database is very large, we used a two-stage method.[17] For each subject in the SCI group, we first randomly sampled 40 age- and sex-matched non-SCI subjects who met the above criteria, giving a total of 476,520 non-SCI subjects. In the second stage, a logistic regression model including age, sex, pre-existing co-morbidities, and socioeconomic status as covariates was used to predict the probability (i.e., propensity score) of SCI. An 8-to-1 digit greedy matching algorithm[10] was then used to identify five matched controls from the non-SCI subjects for each SCI patient according to the propensity score, resulting in a total of 59,565 subjects in the propensity score-matched non-SCI group.

Outcome

All the ambulatory medical care records and inpatient records for each subject in the propensity score–matched SCI and non-SCI groups from their index visit till the end of 2003 were retrieved and mortality data for the subjects who died during follow-up were obtained from the national mortality registry. The date of the first occurrence of a diagnosis of MS (ICD-9-CM codes 340) within the follow-up period was defined as the primary endpoint. The case ascertainment for MS required ≥ 1 hospital discharge or ≥ 2 ambulatory medical care visits with a diagnosis of MS made by a neurologist. All subjects were followed from the index visit to the first occurrence of MS, death, or end of follow-up (whichever occurred first).

Statistical analysis

The chi-square test and Student's *t*-test were used to examine differences in demographic variables, comorbid medical disorders, and propensity score between the SCI and non-SCI groups. The standardized difference method was used to assess covariate balance after propensity score matching; this method is preferred to hypothesis testing methods, as it does not depend on sample size.[18] An absolute standardized difference of 0 for a covariate indicates no between-group imbalance for that covariate and values < 0.1 indicate an inconsequential imbalance.[19] Incidence rates of MS were calculated as the number of incident MS cases divided by the MS-free person-years. Stratified Cox proportional hazard regression with the patients matched by propensity score was used to estimate the effect of SCI on occurrence of MS. An alpha level of 0.05 was considered statistically significant for all analyses. The analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

Results

Table 1 shows the demographic and clinical characteristics for the SCI and non-SCI groups before propensity score matching. The SCI group had a higher prevalence of the pre-existing medical comorbidities diabetes ($p < 0.0001$), hypertension ($p < 0.0001$), and hyperlipidemia ($p = 0.0325$) than the non-SCI group. There also were significant differences in the distribution of monthly income, urbanization level, and geographic region between the SCI and non-SCI groups. After propensity score matching, the matched cohorts were well-balanced in terms of all measured covariates, as

Table 1. Demographic Characteristics and Comorbid Medical Disorders for the Spinal Cord Injury (SCI) and Non-SCI Groups Before Propensity Score Matching

Variable	*SCI group (n = 11,913)*	*Non-SCI group (n = 476,520)*	p *value*
Sex (female)	5814 (48.8)	232,560 (48.8)	1.0000
Age (years)	56.0 ± 17.9	55.8 ± 17.9	0.3215
Diabetes (yes)	1459 (12.3)	44,417 (9.3)	< 0.0001
Hypertension (yes)	3167 (26.6)	107,238 (22.5)	< 0.0001
Hyperlipidemia (yes)	807 (6.8)	29,983 (6.3)	0.0325
Monthly income			< 0.0001
NT$0	3917 (32.9)	130,584 (27.4)	
NT$1-NT$15840	2653 (22.3)	66,047 (13.9)	
NT$15841-NT$25000	4111 (34.5)	189,459 (39.7)	
≥ NT$25001	1232 (10.3)	90,430 (19.0)	
Urbanization level			< 0.0001
1 (most urbanized)	1993 (16.7)	88,108 (18.5)	
2	1393 (11.7)	53,149 (11.1)	
3	2559 (21.5)	120,546 (25.3)	
4	2422 (20.3)	75,090 (15.8)	
5 (least urbanized)	3546 (29.8)	139,627 (29.3)	
Geographic region			< 0.0001
Northern	4668 (39.2)	210,350 (44.1)	
Central	2572 (21.6)	89,351 (18.8)	
Southern	4243 (35.6)	162,750 (34.1)	
Eastern	430 (3.6)	14,069 (3.0)	
Propensity score	0.0287 ± 0.012	0.0243 ± 0.010	< 0.0001

Data are expressed as *n* (%) or mean ± standard deviation.
US $1 = NT$34 in 2001.
NT$, New Taiwan dollar.

Table 2. Demographic Characteristics and Comorbid Medical Disorders for the Spinal Cord Injury (SCI) and Non-SCI Groups After Propensity Score Matching

Variable	*SCI group (n = 11913)*	*Non-SCI group (n = 59565)*	*Standardized difference*
Sex (female)	5814 (48.8)	28,975 (48.6)	0.0032
Age (years)	56.0 ± 17.9	55.6 ± 18.4	0.0230
Diabetes (yes)	1459 (12.3)	7415 (12.4)	0.0061
Hypertension (yes)	3167 (26.6)	15,714 (26.4)	0.0046
Hyperlipidemia (yes)	807 (6.8)	4055 (6.8)	0.0013
Monthly income			0.0342
NT$0	3917 (32.9)	18,980 (31.9)	
NT$1- NT$15840	2653 (22.3)	13,395 (22.5)	
NT$15841-NT$25000	4111 (34.5)	20,467 (34.4)	
≥ NT$25001	1232 (10.3)	6723 (11.2)	
Urbanization level			0.0190
1 (most urbanized)	1993 (16.7)	9662 (16.2)	
2	1393 (11.7)	7104 (11.9)	
3	2559 (21.5)	12,706 (21.3)	
4	2422 (20.3)	12,432 (20.9)	
5 (least urbanized)	3546 (29.8)	17,661 (29.7)	
Geographic region			0.0210
Northern	4668 (39.2)	23,074(38.7)	
Central	2572 (21.6)	13,368 (22.4)	
Southern	4243 (35.6)	20,949 (35.2)	
Eastern	430 (3.6)	2174 (3.7)	
Propensity score	0.0287 ± 0.012	0.0287 ± 0.012	0.0004

Data are expressed as *n* (%) or mean ± standard deviation.
US $1 = NT $34 in 2001.
NT$, New Taiwan dollar.

the absolute standardized differences were all less than 0.1 for all baseline characteristics between the SCI group and matched non-SCI group (Table 2).

The median follow-up time was 30.6 months (interquantile range, 8.8 months). The number of MS events and the hazard ratios (HR) of MS for the two propensity score-matched groups are presented in Table 3. Of the 11,913 patients with SCI, five developed MS during 28,424.2 person-years of follow-up, giving an incidence rate of 17.60 (95% confidence interval [CI], 5.71-41.0) per 100,000 person-years. Of the 59,565 subjects in the non-SCI group, four developed MS during 141,828.7 person-years of follow-up, giving an incidence rate of 2.82 (95% CI, 0.77-7.22) per 100,000 person-years. The HR of MS for the SCI group was therefore 8.33 (95% CI, 1.99-34.87, $p = 0.0037$).

Discussion

In the present population-based, propensity score-matched, longitudinal follow-up study, we found that SCI patients had an 8.33-fold higher risk of MS, compared with non-SCI subjects. Our study is the first to show an increased risk of developing MS in SCI patients. Although the exact mechanism responsible for the association between SCI and MS is unclear, we propose the following explanations.

First, SCI might compromise the blood–spinal cord barrier (BSCB),[20] which in turn, promotes the formation of CNS antigen-specific autoantibodies and neuroinflammation.[21] With a compromised BSCB, the antigens (myelin, phospholipids, and structural proteins) in the brain and spinal cord might leak into the periphery and be exposed to the immune system.[21,22] B and T cells with high affinity for these CNS antigens are then primed in the peripheral lymphoid tissues,[21,23] and, after clonal expansion, B and T cells trafficking to the CNS will re-encounter their specific CNS antigen,[1, 21–23] and release auto-antibodies and produce cytokines[1, 21–23] that will contribute to an inflammation cascade or phagocytic attack on the myelin sheath in the CNS.[1, 21–23]

Second, SCI has been associated with altered systemic autoimmunity. There is evidence that SCI may be related to chronic systemic and intraspinal B cell activation[24] and elevated titers of serum and cerebrospinal fluid autoantibodies to CNS proteins.[24,25] In addition, activation of autoreactive T cells has been shown in

Table 3. Number of MS Events and the Hazard Ratio of MS for the Matched SCI and Non-SCI Groups

Variable	*SCI group (n = 11,913)*	*Non-SCI group (n = 59,565)*
MS events, *n*	5	4
Risk per 100,000 person-years (95% CI)	17.60 (5.71 to 41.0)	2.82 (0.77 to 7.22)
Hazard ratio (95% CI)	8.33 (1.99 to 34.87)*	1.00

*$p = 0.0037$.
MS, multiple sclerosis; SCI, spinal cord injury

SCI.[26,27] Further, experimental studies conducted in transgenic mice have suggested that myelin basic protein–specific autoreactive T lymphoctyes are activated after SCI[28] and are associated with the development of experimental autoimmune encephalomyelitis,[27,28] which is an animal model for human multiple sclerosis.[28] Therefore, these altered immune responses after SCI may contribute to the increased risk of developing MS in patients with SCI.[22,23] Third, previous studies have demonstrated increased psychological stress in patients with SCI,[29,30] and stress has been suggested as a risk factor of MS,[31,32] so the association between SCI and MS might be mediated through SCI-related stress.

Since the present study was a large scale population-based, propensity score–matched, longitudinal follow-up study and the temporal sequence between SCI and MS was ordered, this allowed us to establish a temporal association between SCI and MS. However, several limitations should be addressed. First, the diagnoses of SCI, MS, and medical comorbidities in our study were entirely determined from the ICD codes from the NHI claim database and there may be concern about the diagnostic accuracy of the database. However, the Bureau of the NHI has formed different audit committees that randomly sample the claim data from every hospital and review charts on a regular basis to verify the diagnostic validity and quality of care and, accordingly, the NHI claim database is an established research database and has been used in various biomedical research fields.[33,34]

Moreover, we included only patients who had at least two ambulatory visits with the diagnosis of SCI to optimized case ascertainment. Nevertheless, such case definition is not equivalent to studies administering standardized protocols for the diagnosis of SCI. Second, due to the inherent limitations of the NHI database, information was lacking regarding several lifestyle factors that may have an impact on the risk of MS, such as smoking,[35–37] sunlight exposure,[35,38] and vitamin D consumption,[35,39] which may affect the interpretation of our findings. However, we matched subjects with and without SCI for socioeconomic and geographic characteristics to generate comparable groups. Finally, most inhabitants of Taiwan are of Chinese ethnicity and it is uncertain whether our findings can be generalized to other ethnic groups.

In conclusion, the present population-based, propensity score–matched, longitudinal follow-up study shows that patients with SCI have an increased risk of developing MS. Further studies are required to validate our findings and to investigate the underlying pathophysiological mechanism responsible for the positive association between SCI and MS.

Author Disclosure Statement

This work was supported by grants DOH93-TD-M-113-030, DOH94-TD-M-113-004, and DOH95-TD-M-113-002 from the Department of Health, Executive Yuan, Republic of China, and grant MOST 103-2314-B-002-009 from the Ministry of Science and Technology, Executive Yuan, Republic of China. No competing financial interests exist.

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