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A Nine-Year Population-Based Cohort Study on the Risk of Multiple Sclerosis in Patients with Optic Neuritis

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Patients with optic neuritis (ON) are at an increased risk of developing multiple sclerosis (MS), an illness that may result in physical dysfunction and short life expectancy. Information on the conversion rate to MS of patients with ON is essential in determining the impact of ON on the incidence of MS. Previous Taiwanese studies on the risk of MS in patients with ON were all hospital based, thereby limiting the generalizability of the findings. We aimed to estimate the risk of MS in patients with ON using a nationally representative sample. A cohort of 2,741 patients who sought outpatient care for ON in 2000 was identified from Taiwan's National Health Insurance claims. The control group consisted of 27,330 age- and sex-matched subjects randomly selected from all beneficiaries in 2000. The person-year approach with Poisson assumption was used to estimate the incidence rate of MS from 2000 to 2008. The relative risk of outpatient visit or hospitalization for MS was estimated using the Cox proportional hazard model. The incidence rates of MS in the ON and control groups were 25.6 and 0.4, respectively, per 10,000 person-years; these values represent a relative risk estimate of 30.84 (95% confidence interval: 14.48 to 65.73) after the potential confounders were considered. Female or younger patients with ON were associated with a significantly elevated risk of developing MS. This study found that Taiwanese patients with ON are at a substantially high relative risk of developing MS. In addition to patients with ON, female and younger people should also receive intensive neurological care to further reduce their risk of developing MS.

Keywords: cohort studies; incidence rate; multiple sclerosis; optic neuritis; relative hazard
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Introduction

Demylinating optic neuritis (ON) is an acute inflammation of the optic nerve that mainly occurs in young adults; most patients who present this condition are aged between 20 years to 45 years (Paul et al. 2011). ON usually presents as the first clinical manifestation in about 20% of patients with multiple sclerosis (MS) (Confavreux et al. 2000). In addition, ON can occur during the course of MS, and nearly 66% of patients with MS have optic nerve issues (Rodriguez et al. 1995).

The prevalence of MS is known to be relatively high in high-latitude areas, but the association between temperature and the prevalence of MS has not been clearly established (Taylor et al. 2010). ON is proportionately more common in Asia relative to the incidence of MS in the United States of America or Western Europe (Wakakura et al. 1999). Cumulated studies also found a variable conversion rate to MS of ON patients of various races (Isayama et al. 1982; Optic Neuritis Study Group 1997; Frith et al.

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2000; Ghezzi et al. 2000; Bee et al. 2003; Nilsson et al. 2005; Lin et al. 2006; Chang et al. 2007; Optic Neuritis Study Group 2008). The Optic Neuritis Treatment Trial (ONTT) conducted in the United States found that MS develops in 30% of patients with ON five years after disease onset (Optic Neuritis Study Group 1997). Furthermore, the cumulative probability of developing MS 15 years after the onset of ON increases to 50% (95% confidence interval [CI], 44% to 56%) (Optic Neuritis Study Group 2008). In Australia, 40% of patients with ON were found to develop probable or clinically definite MS after a mean duration of 13.25 years (range, 8 years to 29.6 years) (Frith et al. 2000). A Swedish study reported that the estimated 15-year-risk of MS is 40% (95% CI, 31% to 52%), and that the risk is significantly high in patients with inflammatory cerebrospinal fluid abnormalities at onset (Nilsson et al. 2005). In Italy, a long-term follow-up study evaluated the risk of developing clinically definite MS after acute isolated ON and found that the conversion rate is 13% after 2 years, 30% after 4 years, 38% after 6 years, and 49% after 8 and 10 years (Ghezzi et al. 2000). On the contrary, the conversion rate to MS of patients with ON is significantly low in Asian countries. A hospital-based study found a conversion rate of only 8.3% (mean follow-up, 5.2 years) in Japan (Isayama et al. 1982) and 14.3% to 18.6% in Taiwan (mean follow-up, 4 years to 5 years) (Bee et al. 2003; Lin et al. 2006; Chang et al. 2007). The variability in the above findings may be the result of the differences in patient selection method, diagnostic criteria, geographical factors, duration of follow-up, and study design.

A number of factors explain the link between ON and MS. These factors include abnormal cerebrospinal fluid (CSF) at the onset of ON (Sandberg-Wollheim et al. 1990; Klistorner et al. 2009), certain human leukocytes antigen (HLA) types (Frith et al. 2000; Kheradvar et al. 2004), and brain magnetic resonance imaging (MRI) lesions, which are frequently present in patients with ON (Jin et al. 2003; Optic Neuritis Study Group 2008). A recent study indicated that Tau protein may be a possible prognostic factor in ON and MS (Frederiksen et al. 2012).

The data used in previous Taiwanese studies on the conversion rate to MS of patients with ON were all obtained from a single medical center (Bee et al. 2003; Lin et al. 2006; Chang et al. 2007), and the population-based evidence for the relationship between ON and MS in Taiwan is lacking. Thus, we carried out a population-based cohort study using the Taiwanese National Health Insurance (NHI) database to explore the link between ON and MS. We also sought to update the information on the conversion rate to MS of Taiwanese patients with ON.

Methods

In March 1995, the Taiwan Department of Health integrated 13 health insurance schemes into a universal insurance program, and by 1999, approximately 99% of the 23 million people in Taiwan were enrolled in the NHI Research Database (National Health Insurance Research Database, Taiwan 2010). Experts at the Bureau of National Health Insurance (BNHI) reviews a random sample of every 50 to 100 ambulatory and inpatient medical claims each quarter to ensure data accuracy. Access to research data was approved by the Review Committee of the National Health Research Institutes (NHRI).

The diagnosis of ON was based on clinical criteria, which included acute visual deterioration, pain at or around the eyeball when moving the eye, a relative afferent pupillary defect, and a visual field defect (Roy 1998). Information on all patients who sought ambulatory care for ON (*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 377.3) or were discharged with a primary or secondary diagnosis of ON in 2000 was retrieved from the claim data. After excluding those with prior histories of ON or MS and other demyelinating diseases of the central nervous system (ICD-9-CM 340 and 341) in the period between January 1, 1997 and the date of the first outpatient/inpatient visit (the index date for ON patients) in 2000, a total of 2,741 patients were left and formed the ON group. These patients with ON were deemed as patients with a recent onset of ON and free from MS at the time of their first outpatient/inpatient visit in 2000. We used the frequency matching technique to obtain the control group. In doing so, we first categorized the ON patients and non-ON subjects, respectively, into 42 groups according to 21 age strata (0-4, 5-9, 10-14, 15-19, …… 100-105 years) and 2 genders (male and female). In each age- and sex-specific stratum of the non-ON subjects, we used the simple random sampling method to select control subjects with a non-ON / ON ratio of 10. Because there was an inadequate number of potential controls available in some age- and sex-specific strata, a total of 27,330 controls were selected. These control subjects were also free from ON and MS between January 1, 1997 and January 1, 2000 (the index date for control subjects). The age of each study subject was determined at the time of the index date. The residence of each study subject was classified into levels of urbanization (metropolis, satellite city, or rural area) according to the National Statistics for Regional Standard Classification (Directorate-General Budget, Accounting and Statistics 1993).

To identify possible episodes of MS, all study subjects in both the ON and control groups were linked to the outpatient and inpatient claims from 2000 to 2008 using an encrypted personal identification number (ICD-9-CM 340). Starting in 1983, the diagnosis of MS in Taiwan was based on the Poser criteria (Poser et al. 1983). From 2001 to 2005, the McDonald criteria were followed. Revisions to the McDonald Diagnostic Criteria were proposed in December 2005; they have been used as the guidelines for MS diagnosis thereafter (McDonald et al. 2001; Polman et al. 2005). For those who developed MS by the end of follow-up (i.e., December 31, 2008), the follow-up period was determined as the period between the index date and the date of the detection of MS. For the study subjects who died in the hospital for causes other than MS, the date of censoring was the date of death. For all other subjects, the date of censoring was either the date of their last withdrawal from NHI or the date of study termination (December 31, 2008).

For statistical analysis, we first estimated the age- and sex-specific incidence rate with person-years as the denominator under the Poisson assumption. To determine the independent effect of ON on the risk of developing MS, we constructed Cox proportional hazard regression models with age, sex, and urbanization status adjusted simultaneously in the model. We also adjusted for geographic variables to avoid possible variations in the accessibility to medical treat-

ment. All statistical analyses were performed with SAS (version 9.3; SAS Institute, Chicago, IL). A P value < 0.05 was considered as statistically significant.

Results

The demographic characteristics of the two study groups are shown in Table 1. Female subjects were dominant in both groups. Only 7.2% of patients in both groups were younger than 20 years, and nearly 40% were 40 years to 59 years old. With regard to their residence, the majority of the patients with ON lived in metropolitan areas (43.8%); 42.4% of the control group did so.

Over the nine-year study period, 28 patients with ON developed MS; among these patients, 3 were diagnosed with neuromyelitis optica (ICD-9-CM 341.0). The cumulative rates of overall MS for the ON and control groups were estimated at 1.02% (28/2,741) and 0.04% (9/27,330), respectively (Table 2). Compared with the control group, the ON group showed higher incidence rates of MS, irrespective of sex, age, and urbanization levels. The overall incidence rates of MS for the ON and control groups were 25.6 and 0.4, respectively, per 10,000 person-years. In the ON group, female subjects had an incidence rate of 40.4 per 10,000 person-years; this value was much greater than that (8.0 per 10,000 person-years) of males. However, the control group did not show a high risk of MS in females. With regard to age, the highest incidence rate in the ON group was observed in younger patients aged 20 years to 39 years (62.0 per 10,000 person-years), followed by adolescent patients (34.3 per 10,000 person-years) and those aged 40 years to 59 years (19.0 per 10,000 person-years). Although the age-specific incidence rates were relatively low in the control group, younger people in this group showed high incidence rates of MS. A geographic variation was also observed in the incidence rate of MS among the patients with ON. The patients with ON from metropolitan and rural areas had higher incidence rate of MS than those living in the suburbs of major cities. The very low incidence rate of MS in the control group obscured any geographic variation.

The hazard ratios (HRs) of MS related to the presence of ON and other socio-demographic variables are shown in Table 3. For the patients with ON, the nine-year cumulative incidence rate of MS was 1.02%, which was much higher than the 0.03% rate of the controls. The adjusted hazard ratio (AHR) of developing MS among patients with ON was significantly and substantially increased at 30.84 (95% CI: 14.48 to 65.73, $P < 0.001$). Compared with the males, the female patients were 2.41 times (95% CI: 1.13 to 5.15, $P = 0.023$) more likely to develop MS. Young adult patients had significantly increased AHRs of developing MS (AHR 5.59 [95% CI: 1.24 to 25.13, $P = 0.025$] and 8.23 [95% CI: 2.40 to 28.27, $P = 0.001$] for patients aged < 20 years and those aged 20 years to 39 years, respectively).

Discussion

Although this national study shows a low conversion rate to MS of Taiwanese patients with ON, we found that ON has a strong association with MS. This low conversion rate is similar to that found in several previous reports from Taiwan (Lin et al. 2006; Woung et al. 2007). Previous hospital-based studies indicated that Taiwan is a country with a low risk of MS (Bee et al. 2003; Lin et al. 2006; Chang et al. 2007). In an earlier national study, Tsai et al. reported a prevalence rate of MS in Taiwan of 1.9 per 100,000 (Tsai et al. 2004). In 2005, Lai and Tseng found a high prevalence

Table 1. Characteristics of the study subjects.

Variables	Optic Neuritis Group		Control Group	
	N	%	*n*	%
Sex				
Male	1,252	45.7	12,490	45.7
Female	1,489	54.3	14,840	54.3
Age (years)				
< 20	198	7.2	1,970	7.2
20-39	612	22.3	6,070	22.3
40-59	1,088	39.7	10,860	39.7
> 60	843	30.8	8,430	30.8
Mean ± S.D.[a]	49.0 ± 18.5		49.0 ± 18.5	
Urbanization level				
Metropolis	1,200	43.8	11,601	42.4
Satellite city	690	25.2	7,593	27.8
Rural area	851	31.0	8,136	29.8
Total	2,741	100.0	27,330	100.0

[a]The calculated mean age and standard deviation (S.D.) for Optic Neuritis and Control Groups are 48.96096 ± 18.4943 and 48.9637 ±18.5582, respectively.

Table 2. Incidence rates of multiple sclerosis for the optic neuritis and control groups.

Variables	Optic Neuritis Group				Control Group			
	No. of MS Patients	Observed Person-Years	Incidence Rate[a]	95% CI	No. of MS Patients	Observed Person-Years	Incidence Rate[a]	95% CI
Sex								
Male	4	4,981	8.03	2.19-20.56	6	90,344	0.66	0.24-1.45
Female	24	5,942	40.39	25.88-60.10	3	111,405	0.27	0.06-0.79
Age (years)								
< 20	3	876	34.25	7.06-100.10	1	15,348	0.65	0.02-3.63
20-39	16	2,582	61.97	35.42-100.60	3	44,884	0.67	0.14-1.95
40-59	8	4,210	19.00	8.20-37.44	3	83,777	0.36	0.07-1.05
> 60	1	3,268	3.06	0.08-17.05	2	57,740	0.35	0.04-1.25
Urbanization level								
Metropolis	13	4,757	27.33	14.55-46.73	4	85,904	0.47	0.13-1.19
Satellite city	5	2,704	18.49	6.00-43.15	4	56,177	0.71	0.19-1.82
Rural area	9	3,408	26.41	12.08-50.13	1	59,668	0.17	0.00-0.93
Total	28	10,936	25.60	17.01-37.00	9	201,749	0.45	0.02-0.85

CI, Confidence interval; MS, Multiple sclerosis.
[a]Per 10,000 person-years.

Table 3. Hazard ratios of multiple sclerosis according to presence of optic neuritis, sex, age, and urbanization level.

Variables [a]	*N*	MS		Hazard Ratio Estimates					
		n	%	HR	95% CI	*P*	AHR[b]	95% CI	*P*
Optic neuritis									
No	27,330	9	0.03	1.00			1.00		
Yes	2,741	28	1.02	31.33	14.77-66.46	< 0.001	30.84	14.48-65.73	< 0.001
Sex									
Male	13,739	10	0.07	1.00			1.00		
Female	16,324	27	0.17	2.28	1.10-4.70	0.027	2.41	1.13-5.15	0.023
Age									
< 20	2,168	4	0.18	5.71	1.28-25.54	0.023	5.59	1.24-25.13	0.025
20-39	6,682	19	0.28	8.81	2.61-29.79	0.001	8.23	2.40-28.27	0.001
40-59	11,948	11	0.09	2.85	0.79-10.21	0.108	2.71	0.75-9.79	0.127
> 60	9,273	3	0.03	1.00			1.00		
Urbanization level									
Metropolis	12,790	17	0.13	1.19	0.55-2.61	0.658	0.98	0.44-2.16	0.956
Satellite city	8,277	9	0.11	0.98	0.40-2.40	0.958	0.90	0.36-2.23	0.812
Rural area	8,976	10	0.11	1.00			1.00		
Total	30,071	37	0.12						

AHR, Adjusted hazard ratio; CI, Confidence interval; HR, Hazard ratio; MS, Multiple sclerosis.
[a]The inconsistency between total population and population sum for individual variable is due to missing information.
[b]Estimated from multivariate logistic regression with optic neuritis, sex, age, and urbanization level simultaneously included in the model.

of MS in Taiwan, but it was still low at 2.96 per 100,000 (Lai and Tseng 2009); this finding is similar to that noted in several Asian countries (Kira 2003). Lin et al. also found a low conversion rate to MS among Taiwanese patients with idiopathic ON, with a 5.92%, two-year cumulative probability and a 14.28%, five-year cumulative probability of developing MS (Lin et al. 2006).

Although the etiology of the ON-MS relationship remains unclear, ON may interact with MS multifactorially, including through geographic, genetic, and environmental vectors (Kira 2003). A large-scale clinical study in Taiwan enrolled 109 patients with ON with a mean follow-up of

five years. In the study, the following factors were found to be associated with an increased risk of MS: female gender, retrobulbar ON, abnormal central nervous system MRI, and cerebrospinal fluid immunoglobulin (Ig) G index (Lin et al. 2006). Female patients with ON are known to have a higher risk for developing MS compared with males (Optic Neuritis Study Group 1991; Noseworthy et al. 2000; Milo and Kahana 2010). Consistent with some previous studies, our results also show that female patients with ON have a greater risk of progressing to MS compared with males (female vs. male: 40.4 vs. 8.0 cases per 10,000 person-years). In the ONTT study, the risk of MS was found to be three times higher in female patients with ON than in their male counterparts (Optic Neuritis Study Group 2008). With regard to the pathomechanism of the effect of gender on MS, sex hormone or sex-linked genetic factors may play a role. One study on early onset MS (clinical onset before 16 years) found that male patients younger than 12 years of age are more likely to develop MS compared with their female counterparts (Ghezzi et al. 2002). These findings indicate that hormone change may influence disease susceptibility (Ghezzi et al. 2002).

In addition, the female-to-male ratio in patients with MS has been increasing for the last 50 years (Orton et al. 2006; Houzen et al. 2012; Trojano et al. 2012). As genetic factors are unlikely to change sex ratios over such a short time, environmental factors such as increased outdoor activity and alterations in diet may be responsible for such change (Sadovnick 2009). Similar to ours, the findings of several recent studies also reveal a gender difference in the conversion rate to MS of patients with ON, with a higher rate noted for females than for males (Houzen et al. 2012; Trojano et al. 2012).

We noted that the incidence rate of MS among the patients with ON in our study peaked at the ages of 20 years to 39 years. We also noted that those aged 39 years or younger were at an increased risk (AHR range, 5.59 to 8.23) of MS compared with the older patients (> 60 years). Such findings are in agreement with the data reported in most previous studies (Sandberg-Wollheim et al. 1990; Frith et al. 2000; Jin et al. 2003; Klistorner et al. 2009), except the data in the study by Bradley and Whitty (Bradley and Whitty 1968), who found a greater risk of MS in older patients with ON. The reasons for the effect of age on the risk of MS are still unclear. Some experts speculate that a specific HLA genotype is related to age at MS development (Qiu et al. 2010). As MS is generally thought to be an autoimmune disease, certain immunogenetic factors may also likely account for a higher risk of MS in younger people than in older ones.

Our study has certain methodological strengths. First, we used the NHI dataset, a representative national sample that minimizes the chance of selection bias resulting from non-response or loss to follow-up of study subjects. Second, the large number of study subjects allowed us to conduct detailed analyses of variables of interest (e.g., age, sex, and level of urbanization).

However, the present study also has several limitations. First, some studies reported that most patients develop MS within four years of the onset of ON (Frith et al. 2000; Klistorner et al. 2009), but others indicated that ON patients may have conversion many years later (Francis et al. 1987). Therefore, the length of follow-up for the subjects involved in our study may be inadequate and thus lead to an underestimation of the conversion rate. Second, etiologies of ON other than demyelination could not be identified from the claim data; this drawback may also result in the underestimation of the true relative hazard. Nevertheless, the conversion rate to MS of Taiwanese patients with ON remains considerably low because demyelination is the major cause of ON (approximately 68% in a study from Japan [Wakakura et al. 1999] and 75% in a study from Singapore [Lim et al. 2008]). Third, our study covered a nine-year follow-up period within which the diagnostic criteria for determining MS changed over time, thus resulting in potential information bias. As the inaccuracy in MS diagnosis, if any, could happen to patients with and without ON, the potential information obtained in our study is likely to be non-differential and may thus result in the underestimation of relative risk estimates (Jurek et al. 2008). Lastly, the NHI claims do not contain clinical parameters, such as MRI, electrodiagnostic examinations, CSF findings, or immunogenetic characteristics. In addition, information on family disease history and laboratory examination data, such as macular star figure and optic disc edema, may confound the study findings. For example, an abnormal MRI is believed to be a valuable predictor for the later development of MS (Jacobs et al. 1997).

Although the conversion rate to MS was found to be rather low in Taiwanese patients with ON, this population-based cohort study still confirms a substantial and significant association between ON and MS. We noted an increased risk of MS among females and younger patients with ON. We also found that age and sex were significant predictors (independent of ON) of the risk of MS. Vigilance is necessary in monitoring the progression of ON in high-risk populations. Clinicians should also consider providing aggressive treatments for these high-risk populations.

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Conflict of Interest

The authors declare no conflict of interest.

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