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Original Research Paper

Prevalence and incidence of neuromyelitis optica spectrum disorder and multiple sclerosis in Korea

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Abstract

Background: The epidemiology of neuromyelitis optica spectrum disorder and multiple sclerosis varies depending on the region and ethnicity.

Objective: To estimate the prevalence and incidence of neuromyelitis optica spectrum disorder and multiple sclerosis in Korea during 2010–2016.

Methods: We analyzed the National Health Insurance research database, which contains single-payer health insurance data collected in Korea. Neuromyelitis optica spectrum disorder was defined based on the 2006 Wingerchuk criteria (for 2010–2015), and the 2015 International Panel for Neuromyelitis Optica Diagnosis criteria (for 2016). Multiple sclerosis was defined by the 2005 International Panel criteria for multiple sclerosis.

Results: In 2016, the age-standardized prevalence per 100,000 persons was 2.56 (95% confidence interval: 2.43–2.7) for neuromyelitis optica spectrum disorder and 3.23 (95% confidence interval: 3.08–3.39) for multiple sclerosis. The age-standardized incidence of neuromyelitis optica spectrum disorder and multiple sclerosis were 0.73 (95% confidence interval: 0.66–0.8) and 0.50 (95% confidence interval: 0.44–0.56) per million in 2016. The prevalence of neuromyelitis optica spectrum disorder and multiple sclerosis have increased over time during 2010–2016 (18.5% and 5.4% annually; both p-trend < 0.001). The incidence of neuromyelitis optica spectrum disorder increased annually (10.0%, p-trend < 0.001), while the incidence of multiple sclerosis remained stable.

Conclusion: While the prevalence of neuromyelitis optica spectrum disorder and multiple sclerosis are comparable in Korea, the incidence of neuromyelitis optica spectrum disorder is higher than that of multiple sclerosis. Both the prevalence and incidence of neuromyelitis optica spectrum disorder are rapidly increasing in Korea.

Keywords: Multiple sclerosis, neuromyelitis optica spectrum disorder, prevalence, incidence, Asia, epidemiology

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Introduction

Inflammatory demyelinating diseases of the central nervous system (CNS) represent a heterogeneous group of disorders among which multiple sclerosis (MS) accounts for the vast majority in Western countries. Neuromyelitis optica spectrum disorder (NMOSD) is a chronic, recurrent inflammatory demyelinating disease that frequently involves the spinal cord, optic nerves and specific brain lesions, such as those in the area postrema.[1] Since the discovery of anti-aquaporin-4 antibodies (AQP4-Ab), NMOSD has been regarded as a specific entity with pathological, radiological, and clinical features that are broadly different from those observed in MS.[1,2]

The prevalence and incidence of NMOSD and MS seem to vary according to race, geographic location and estimated period.[3–6] Several recent cohort and hospital-based studies have suggested that the relative prevalence of NMOSD to MS may be high in Asia.[3,5,7] Nevertheless, not enough nationwide population-based studies have evaluated the incidence and

prevalence of NMOSD and MS in this region. Hence, we aimed to estimate the incidence and prevalence of NMOSD and MS in Korea using the nationwide population-based database of the National Health Insurance (NHI) system.

Materials and methods

A nationwide dataset available in the National Health Insurance Research Database (NHIRD) was used for this study. The Republic of Korea is located in Eastern Asia (latitudes between 33°06 N and 38°15 N), and the population reached 51,827,813 (almost half of the population lives in the metropolitan area) in 2016.[8] The ethnicity of Korea is highly homogeneous with such low levels of immigration and emigration that more than 98% of the population are ethnic Koreans.[9] In the Republic of Korea, the government has implemented a single-payer NHI system that covers the entire population. All health care institutions submit claims data to the Korean NHIS for the reimbursement of services provided, including diagnosis codes classified by the International Classification of Diseases, 10th revision (ICD-10), diagnostic tests and therapeutic procedures performed during admission and ambulatory care, and prescription records. Therefore, the claims data of all Korean patients at all health care institutions are prospectively integrated into the Korean NHIS database.

The NHI has run the Rare Intractable Diseases (RID) registration program since 2009 to apply reduced copayments for the diagnosis and treatment of RIDs. Patients are required to submit official certificates written by physician that testifies to their RID diagnosis; these must be based on the diagnostic criteria distributed by the NHI. The NHI checks the application again if the patients meet the proper criteria. Therefore, almost all patients apply for this program to obtain financial benefits, and the administrative process ensures that diagnoses of RIDs are highly reliable. MS has been registered in the RID system since 2009, and NMOSD has been registered since 2016. The RID registration for NMOSD was based on the 2015 International Panel for NMO Diagnosis (IPND) criteria for NMOSD.[1] The inclusion of cases of MS as a RID must meet the 2005 international panel criteria for MS.[10]

We used NHIRD data obtained from 1 January 2010 to 31 December 2016 based on the introduction of the RID system. NMOSD was defined when any of the following criteria were met: (1) ⩾2 outpatient or hospitalization claims with the ICD-10 code (G360) or (2) registration in the RID registration system with the code for NMOSD. Diagnoses based on RID codes have been confirmed to be more valid than those based on other insurance data.[11] Because NMOSD has only been included as an RID since 2016, NMOSD was defined according to the 2006 Wingerchuk criteria until 2015, and with the 2015 revised criteria starting in 2016.[1,12] MS was defined as registration in the RID registration system with MS-related codes without satisfaction of the definition of NMOSD, as outlined above. This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. E-1808-057-964).

Annual prevalence and incidence were calculated as previously described.[9] Direct standardization by age and sex was computed using the mid-year population for 2010. Trends over time were analyzed using Poisson regression. The female to male incidence ratio was estimated for each year using Poisson regression and is presented as the age-adjusted incidence rate ratio (IRR). Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Prevalence and incidence of NMOSD and MS in 2016

The age- and sex-standardized prevalence and incidence of NMOSD and MS in 2016 are shown in Table 1. There was no significant difference in the age distributions of newly diagnosed cases of NMOSD and MS in 2016. A female predominance was observed in the prevalence and incidence of both NMOSD and MS, but the difference was more marked in NMOSD (3.98 per 100,000 vs 2.74 per 100,000, respectively, for prevalence; 1.0 per 100,000 vs 0.45 per 100,000, respectively, for incidence; $p < 0.05$). The prevalence and incidence of NMOSD and MS reported in 2016 are shown according to age and sex in Figure 1.

Trends in the prevalence and incidence of MS and NMOSD from 2010–2016

From 2010 to 2016, 1978 NMOSD and 1952 MS patients were newly diagnosed in Korea. The annually calculated crude-, age- and sex-standardized prevalence and incidence of NMOSD and MS from 2010 to 2016 are shown in Table 1. The prevalence of NMOSD increased linearly 18.5% (95% confidence interval (CI): 17.13%–19.8%; p for trend < 0.001), while that of MS increased 5.4% (95% CI: 4.42%–6.34%; p for trend < 0.001) (Figure 2) each year. The incidence of NMOSD showed a 10.0% annual

Table 1. Annual prevalence and incidence of neuromyelitis optica spectrum disorder and multiple sclerosis during 2010–2016.

Year	Prevalence				Incidence			
	Total population	Number of prevalent cases	Crude PR[a] (95% CI)	Standardized PR[a,b] (95% CI)	Total population	Number of incident cases	Crude IR[a] (95% CI)	Standardized IR[a,b] (95% CI)
NMOSD								
2010	50166793	375	0.75 (0.68–0.83)	0.75 (0.67–0.83)	50166401	173	0.35 (0.3–0.4)	0.35 (0.29–0.4)
2011	50445164	534	1.06 (0.97–1.2)	1.05 (0.97–1.14)	50444606	236	0.47 (0.41–0.53)	0.47 (0.41–0.53)
2012	50763154	684	1.35 (1.3–1.5)	1.34 (1.24–1.44)	50762375	239	0.47 (0.41–0.53)	0.47 (0.41–0.53)
2013	51013675	883	1.73 (1.6–1.8)	1.78 (1.60–1.82)	51012664	332	0.65 (0.58–0.72)	0.64 (0.57–0.71)
2014	51281917	962	1.88 (1.8–2)	1.84 (1.72–1.95)	51280588	324	0.63 (0.57–0.7)	0.62 (0.55–0.69)
2015	51574044	1082	2.1 (2–2.2)	2.05 (1.93–2.17)	51572412	287	0.56 (0.5–0.62)	0.55 (0.48–0.61)
2016	51827813	1365	2.63 (2.5–2.8)	2.56 (2.43–2.7)	51825929	387	0.75 (0.68–0.83)	0.73 (0.66–0.8)
MS								
2010	50166793	1194	2.38 (2.2–2.5)	2.34 (2.24–2.51)	50162633	267	0.53 (0.47–0.6)	0.53 (0.46–0.59)
2011	50445164	1339	2.65 (2.5–2.8)	2.63 (2.49–2.78)	50440845	272	0.54 (0.48–0.61)	0.54 (0.47–0.60)
2012	50763154	1404	2.77 (2.6–2.9)	2.73 (2.58–2.87)	50758648	238	0.47 (0.41–0.53)	0.46 (0.41–0.52)
2013	51013675	1605	3.15 (3.0–3.3)	3.08 (2.93–3.23)	51009010	346	0.68 (0.61–0.75)	0.66 (0.59–0.73)
2014	51281917	1577	3.08 (2.9–3.2)	3.01 (2.86–3.16)	51276996	224	0.44 (0.38–0.5)	0.43 (0.37–0.48)
2015	51574044	1700	3.3 (3.1–3.5)	3.2 (3.05–3.36)	51568958	341	0.66 (0.59–0.73)	0.64 (0.57–0.71)
2016	51827813	1726	3.33 (3.2–3.5)	3.23 (3.08–3.39)	51822474	264	0.51 (0.45–0.57)	0.5 (0.44–0.56)

CI: confidence interval; IR: incidence rate; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; PR: prevalence rate.
[a]The crude and standardized prevalence and incidence rates per 100,000 persons are shown.
[b]Age- and sex-standardized values for the 2010 population are presented.

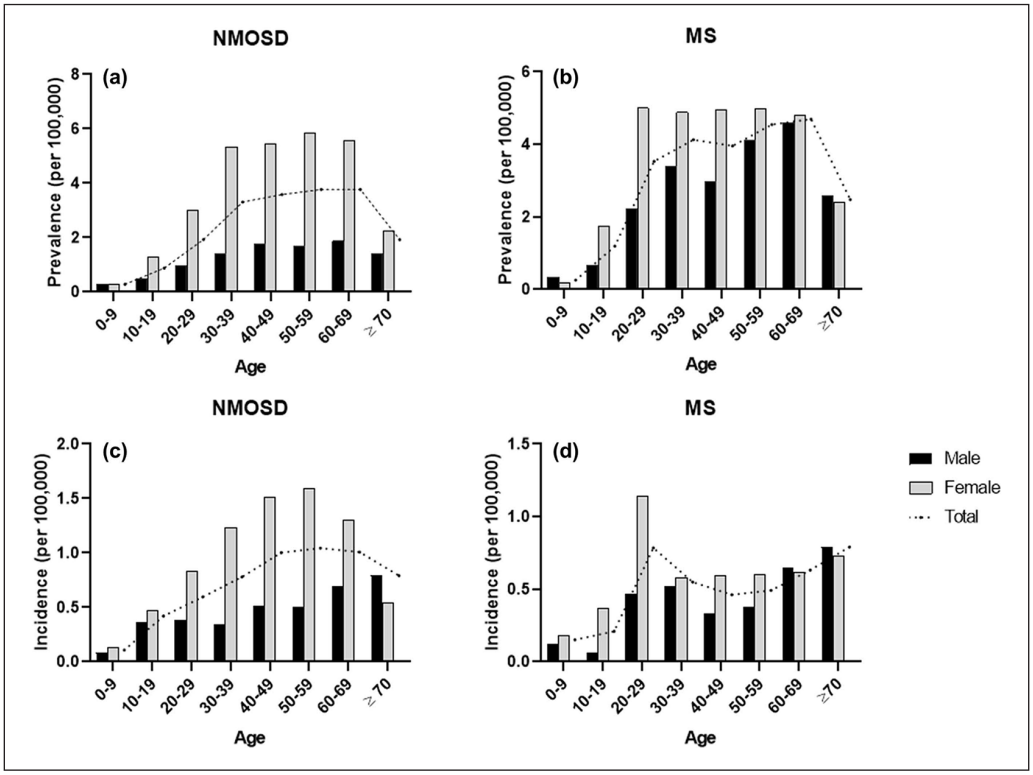

Figure 1. Prevalence and incidence of neuromyelitis optica spectrum disorder and multiple sclerosis. The sex- and age-specific (a and b) prevalence and(c and d) incidence of NMOSD and MS in 2016 are shown.
MS: multiple sclerosis; NMOSD: neuromyelitis optical spectrum disorder.

increase (95% CI: 7.8%–12.27%; p for trend < 0.001). However, the incidence of MS did not significantly change during the study period.

Women have a higher risk than was found in men of developing NMOSD and MS during 2010–2016. The IRR of females to males ranged from 1.76 to 2.37 for NMOSD and 0.91 to 1.79 for MS. The female preponderances observed in NMOSD and MS seem to have arisen more recently, but the time-trend changes for these gender deviations were not statistically significant (Table 2).

Discussion

This is the first nationwide survey performed in Korea to evaluate the prevalence and incidence of both NMOSD and MS in collinear comparisons. Their prevalence and incidence in 2016 are especially noteworthy because that is when NMOSD was initially registered in the highly reliable RID system according to an adoption of the 2015 IPND diagnostic criteria for NMOSD.[1,11]

The prevalence and incidence of NMOSD in Korea are estimated to have been 2.56 and 0.73 per 100,000, respectively, in 2016. Our prevalence rate is within the previously reported range of 0.9–4.1 per 100,000 in Asia.[7,13–16] However, the incidence rate of NMOSD was remarkably higher in our study than has been reported elsewhere in Asian and Caucasian populations but similar to that reported in Martinique.[15,17] NMOSD is known to have ethnical partiality for non-Caucasians.[18–20] Among CNS demyelinating diseases, NMOSD accounts for only 2% in Caucasians but 15%–57% in Japanese, Iran and African-American populations.[18–20] Likewise, the prevalence and the incidence of NMOSD show regional and ethnical variations. Genetic differences among races, environmental factors (such as latitude), and exposure to infections might contribute to these differences.[6]

In our study, in 2016, the standardized prevalence and incidence of MS in Korea were 3.23 and 0.50 per 100,000 inhabitants, respectively, after NMOSD was excluded. This is slightly lower than the results of a previous report (3.5–3.6 per 100,000).[21] We speculate that this slight decrease in the prevalence of MS might stem from the correct classification of NMOSD and MS as the phenotypes of NMOSD can sometimes mimic MS, and patients with a concomitant diagnosis of NMOSD were excluded from the MS group in our study.

The prevalence of MS in Korea is considerably lower than that reported in North America and Europe (more than 100 cases per 100,000) and comparable to other reports obtained in Asian countries with a low prevalence of MS (less than 10 cases per 100,000), with the exception of Japan (up to 16.2 cases per 100,000).[3,4,7,13,22,23] It is worth noting that the prevalence of MS is three times higher in Japan than in Korea despite the geographically close locations of these two countries. Genetic susceptibility, such as human leukocyte antigen polymorphisms, latitude and Vitamin D levels, have been suggested to contribute to these regional variations.[6]

The prevalence and incidence of NMOSD have increased rapidly over the years in Korea. Increased awareness of NMOSD, increased AQP4-Ab seropositive status due to the accessibility of AQP4-Ab assay and the application of the more sensitive 2015 IPND criteria could also be major reasons for these findings. In Korea, assays for AQP4-Ab for research purpose were started in 2009 by foreign laboratory and soon became established as in-house live and/or fixed cell

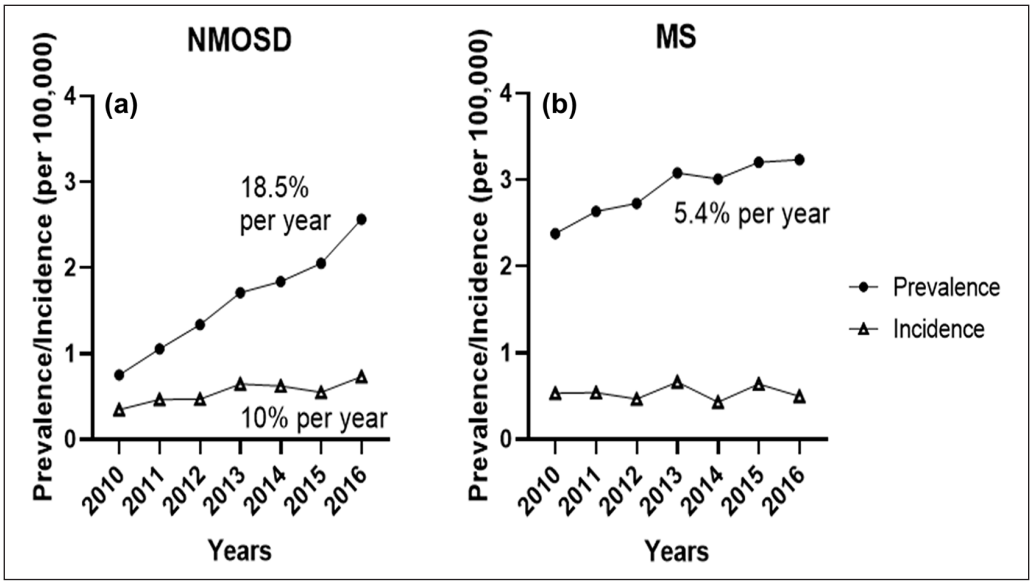

Figure 2. Trends in the annual prevalence and incidence of NMOSD (a) and MS (b) during 2010–2016. The prevalence increased 18.5% and 5.4% annually for NMOSD and MS, respectively (both, p-trends < 0.001). The incidence of NMOSD showed a 10.0% annual increase (p-trends < 0.001). The prevalence per 100,000 of each year is marked as a black circle, and the incidence per 100,000 is indicated as empty triangles.
MS: multiple sclerosis; NMOSD: neuromyelitis optical spectrum disorder.

Table 2. Female to male incidence rate ratios of neuromyelitis optica spectrum disorder and multiple sclerosis during 2010–2016.

Year	NMOSD				MS			
	Incidence (per 100,000)		IRR (95% CI)		Incidence (per 100,000)		IRR (95% CI)	
	Male	Female	Crude IRR	Age-adjusted IRR	Male	Female	Crude IRR	Age-adjusted IRR
2010	0.24	0.45	1.85 (1.35–2.52)	1.85 (1.36–2.53)	0.51	0.56	1.092 (0.85–1.39)	1.06 (0.83–1.34)
2011	0.32	0.61	1.89 (1.44–2.47)	1.90 (1.45–2.48)	0.46	0.62	1.33 (1.05–1.69)	1.29 (1.02–1.64)
2012	0.30	0.64	2.15 (1.64–2.83)	2.17 (1.65–2.84)	0.40	0.54	1.34 (1.04–1.73)	1.30 (1.01–1.68)
2013	0.45	0.85	1.87 (1.49–2.34)	1.88 (1.50–2.36)	0.70	0.66	0.94 (0.76–1.16)	0.91 (0.74–1.12)
2014	0.44	0.82	1.82 (1.45–2.29)	1.84 (1.46–2.31)	0.31	0.57	1.84 (1.40–2.42)	1.79 (1.36–2.35)
2015	0.41	0.71	1.74 (1.37–2.21)	1.76 (1.38–2.23)	0.59	0.74	1.26 (1.02–1.56)	1.23 (0.99–1.52)
2016	0.45	1.00	2.34 (1.88–2.91)	2.37 (1.90–2.94)	0.40	0.62	1.54 (1.20–1.97)	1.50 (1.17–1.92)

CI: confidence interval; IRR: incidence rate ratio; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder.

assay by several referred centers.[24–26] The in-vitro diagnostic AQP4-Ab assay for medical use was approved by the Korean Ministry of Health and Welfare in 2015 (fixed cell based assays) and 2016 (flow cytometric live-cell assays in 2016), respectively.[27]

In Korea, the prevalence of MS is tending to increase over time without any change in its incidence. Established treatments and reductions in the mortality of MS are possible reasons for this finding. The trends toward an increased prevalence and/or incidence of MS are observed worldwide.[28,29] Some serial reports from areas with relatively few immigrants support the hypothesis that environmental factors, such as hygiene, food, and lifestyle, may affect immunological conditions and MS development.[30] The constant incidence of MS in our study may have been influenced by a relatively shorter study period.

Interestingly, the patterns of distribution in the frequencies of MS prevalence and incidence show some discrepancies between the sexes. In addition, the incidence patterns along ages are somewhat different between NMOSD and MS. This might suggest that MS and NMOSD are not identical and that their clinical features may be different depending on the sex even in same disease. Men are known to have a later onset of MS, more progression of disability and a slightly higher prevalence of a primary progressive course than is observed in women.[31]

In our study, the female-to-male ratio of NMOSD (2.37:1) and MS (1.5:1) were relatively lower than those reported worldwide.[3,5,6] A relatively low female-to-male ratio was consistently observed for MS in previous nationwide epidemiological study performed in Korea and in studies performed in other Asian countries.[7,21,32] The cause of the relative higher proportion of males with NMOSD and MS in our study is unclear. However, genetic and environmental factor and the latitude of studied region may had an influence.[29] Moreover, seronegative NMOSD was also included in our study, a considerable number of whom may have myelin oligodendrocyte glycoprotein-IgG associated encephalomyelitis (MOG-EM) or other autoimmune causes. MOG-EM is known to have less or no female preponderance.[33] A recent study performed in Korea that only included seropositive NMOSD showed that the female-to-male ratio was 4.7:1, which is higher than the findings of the current study.[34]

Notably, peak incidence of NMOSD is observed in older age in our study. This might be related to our study method to define incidence based on date of diagnosis rather than date of symptom onset due to the restricted information available in the NHIRD. NMOSD is frequently misdiagnosed as MS, and its diagnosis tends to be delayed.[35] In the same context, the unusual high incidence of MS in the elderly in our study may be due to the late diagnosis of a population with an earlier onset. The registration of MS in the RID system began in 2006, and a fair number of MS cases may have been registered a considerable time after diagnosis.

Due to our unique NIH with RID system, our data represent a reliable epidemiological record of MS and NMOSD that includes almost the entire Korean population and takes advantage of multiple sources of ascertainment of their diagnoses. The prevalence and incidence rates of NMOSD and MS are comparable in Korea, although the incidence of NMOSD in Korea is increasing, while the incidence of MS remains stable over time.

Authors' Note

Statistical analysis was conducted by Sang-hyun Park and Kyungdo Han, who had their affiliation on department of Medical Statics, College of Medicine, The Catholic University of Korea, Seoul, Korea.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S.M.K. has lectured, consulted, and received honoraria from Bayer Schering Pharma, Genzyme, Merck Serono, and UCB; received a grant from the National Research Foundation of Korea and the Korea Health Industry Development Institute Research; is an Associated Editor of the *Journal of Clinical Neurology*. S.M.K. and Seoul National University Hospital has transferred the technology of flow cytometric AQP4-Ab assay to EONE Laboratory, Korea. H.J.K. has lectured, consulted and received honoraria from Bayer Schering Pharma, Biogen, Celltrion, Eisai, HanAll BioPharma, MedImmune, Merck Serono, Novartis, Sanofi Genzyme, TevaHandok and UCB; received a grant from the Ministry of Science and ICT; accepted research funding from Sanofi Genzyme, Teva-Handok and UCB; serves on a steering committee for MedImmune; is a co-editor for the *Multiple Sclerosis Journal—Experimental, Translational, and Clinical* and an associated editor for the *Journal of Clinical Neurology*. JE Kim, SH Park, KD Han and DW Shin declare that there is no conflict of interest.

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