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Clinical trial

Changing patterns of multiple sclerosis in Korea: Toward a more baseline MRI lesions and intrathecal humoral immune responses

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ABSTRACT

Background: The environmental risks of multiple sclerosis (MS), including adolescent obesity and vitamin D deficiency, are increasing in Korea. We aimed to determine whether the patterns and/or severity of MS in Korea can change according to the year of birth or disease onset.

Methods: Two hundred and sixty-six patients with adult-onset MS, including 164 with an available baseline magnetic resonance imaging (MRI), were retrospectively included from 17 nationwide referral hospitals in Korea. The demographics, MRI T2 lesion burden at disease onset, cerebrospinal fluid markers, and prognosis were assessed.

Results: The birth year, time from disease onset to first MRI, and female sex were associated with a higher number of baseline MRI T2 lesions. The birth year was also associated with the presence of oligoclonal band in the cerebrospinal fluid and high immunoglobin G index. An increased female/male ratio was observed among those with a more recent year of birth and/or disease onset.

Conclusions: In Korea, the disease pattern of adult-onset MS may be changing toward a more baseline T2 MRI lesions, intrathecal humoral immune responses, and also higher female ratio.

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1. Introduction

Korea has been considered to be a low risk areas for multiple sclerosis (MS) (Browne et al., 2014; Kim et al., 2010). However the environmental risks for MS, including adolescent obesity, vitamin D insufficiency, and urbanization are rapidly increasing in it (Choi et al., 2011; Ha and Kim, 2016; Kim and Kim, 2011). Recent epidemiological studies has shown that the environmental changes in a genetically stable population can affect the pattern and severity of MS (Berg-Hansen et al., 2013; Kotzamani et al., 2012; Thompson et al., 2017).

The aim of this study is to evaluate whether the patterns and severity of MS in Korea are changing according to the year of birth or disease onset, based on nationwide hospital-based multicenter cohort data.

2. Methods

2.1. Patients

Two hundred and sixty-six patients with relapsing-onset MS according to the international panel criteria (Thompson et al., 2017), who had a disease onset at 18 years of age or older and did not meet international consensus criteria for neuromyelitis optica spectrum disorder (NMOSD) (Wingerchuk et al., 2015), were retrospectively included from 17 nationwide referral hospitals in Korea. All cases were reassessed for the diagnosis of MS by two MS/NMOSD experts (HJK and SMK). The demographics, number/rate of attacks, presence of cerebrospinal fluid (CSF) OCBs by isoelectric focusing (IEF), CSF immunoglobin G (IgG) index, and time to first relapse after initial DMT were assessed. A relapse was defined as a clinical episode with patient-reported symptoms and objective findings typical of MS with a duration of at least 24 h (Thompson et al., 2017). A CSF IgG index of >0.67 was considered high (Rudick et al., 1999).

2.2. Assessment of baseline T2-weighted brain MRI lesions

Baseline MRI was defined as an initial brain MRI performed after disease onset, but before the onset of the second attack. The number of T2 lesions of at least 3 mm in their largest linear measurement were counted (Traboulsee et al., 2016). Among 266 patients, 164 (61.7%) had available baseline brain MRI scans. An experienced neurologist at each referral hospital participated as an independent rater of the T2 lesion counting of his/her own patients. Inter-rater agreement was confirmed by an intraclass correlation between the three representative raters (HJS, JWH, and SMK). The sample MRI set for inter-rater agreement was extracted by systematic sampling as follows: the baseline datasets of the 164 patients were sorted by the number of T2 lesions, and the sample elements were selected with a sampling interval of five. Inter-rater agreement for T2 lesion counting between the three representative raters was excellent in terms of the intraclass correlation coefficient, 0.965 (95% confidence interval [CI]: 0.928–0.983) (Cicchetti, 1994). The intraclass correlation coefficient for each pair of raters was 0.958 (HJS and SMK), 0.975 (HJS and JWH), and 0.962 (JWH and SMK).

2.3. Risk of relapse after initial disease modifying treatment

The time to first relapse after the use of the initial disease modifying treatment (DMT) was assessed. The records indicating the type of initial DMT were available for 253 patients, while the date of prescription and date of first relapse after initial DMT were available for 236 patients. To minimize the effect of differences in potency for each DMT on the risk of relapses (Fogarty et al., 2016), subgroup analyses for the first line DMTs with similar efficacy (an annualized relapse rate reduction between 33 and 36%; either interferon beta-1b subcutaneous (SC), interferon beta-1a SC, glatiramer acetate, or Teriflunomide) (Fogarty et al., 2016) were also performed ($n = 216$).

2.4. Risk of disease progression

Disability was graded according to the Kurzje Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). A score was confirmed when it was irreversible for more than 6 months and up to the last visit (Leray et al., 2010). The time from onset to confirmed EDSS of 4 or 6 was assessed, respectively.

2.5. Statistical analysis

Multivariable Poisson regression analysis and binary logistic regression analysis were performed to identify the factors associated with the T2-weighted brain MRI activity at disease onset and CSF OCB positivity/high IgG index, respectively. Multicollinearity was assessed by variance inflation factors (VIF) and variables with a VIF ≤ 5 were included in the analysis (Vatcheva et al., 2016). The Cox proportional hazard regression model was used to assess the risk of relapse after initial first line DMT and/or risk of disease progression. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software V.22.0.

2.6. Standard protocol approval, registration, and patient consent

This study was approved by the institutional review board of the National Cancer Center (IRB number: NCC2014-0146) and Seoul National University Hospital in Korea (approval number: H-1012-080-344). As a retrospective anonymized review of medical records, informed patient consent was waived.

3. Results

3.1. Demographics

A total of 266 patients (171 females) were recruited from 17 MS referral hospitals. The demographic data and clinical characteristics are shown in Table 1.

3.2. Baseline brain T2 lesion number: association with the year of birth

The univariate Poisson regression analysis revealed that the year of birth, female sex, time from disease onset to baseline MRI, the year of disease onset, and the year of baseline MRI were associated with the baseline brain MRI T2 lesion number (Table 2). Among these variables, the year of disease onset and the year of baseline MRI were highly intercorrelated ($R^2 = 0.726$). Two multivariable models were developed to avoid multicollinearity issues. In the multivariable analysis using models 1 and 2, the year of birth, female sex, and time from disease onset to baseline MRI were independently associated with the baseline brain MRI T2 lesion numbers. Neither the year of disease onset nor the year of baseline MRI was associated with the number of baseline T2 MRI lesions (Fig. 1 and Table 3).

3.3. Intrathecal humoral immune response and year of birth

Both the OCB positivity by IEF and the proportion of high CSF IgG indices tended to be higher in later born patients. A positive OCB and the presence of a high IgG index was observed in only 20 and 13% of patients born in 1950s, but increased to 54 and 75% among patients born in the 1990s, respectively (Fig. 2). Neither OCB positivity nor the presence of a high IgG index were associated with the year of disease onset ($p = 0.277$ and 0.051, respectively).

3.4. Female ratio according to the year of birth or disease onset

The ratio of females to males showed a trend toward an increase with a more recent year of birth and disease onset. The female ratio was

Table 1
Demographic data and clinical characteristics.

	n = 266
Female: male (female %)	171:95 (64.3%)
Age at onset, years*	30.8 ± 8.4
Year of birth*	1978 ± 9.3
Year of onset*	2009 ± 5.6
Follow-up duration, years*	5.53 ± 3.82
Cumulative number of attacks*	3.12 ± 2.19
ARR per year*	0.70 ± 0.94
Number of T2 lesions at disease onset[c]*	15.9 ± 15.4
CSF study	
IgG index >0.67 (%)	115/212 (54.0%)
OCB positive (%)[d]	54/125 (43.2%)
IgG index >0.67 or OCB positive by IEF (%)[d]	125/165 (75.8%)
Types of initial DMT (n = 253)	
Any INFb	227 (90%)
SC INFb-1b	124 (49.0%)
SC INFb-ab	91 (36.0%)
IM INFb-1a	12 (4.7%)
Glatiramer acetate	8 (3.2%)
Teriflunomide	7 (2.8%)
Dimethyl fumarate	5 (2.0%)
Fingolimod	4 (1.6%)
Natalizumab	1 (0.4%)
Time to first relapse after initial DMT, years[b]*	1.22 ± 1.96
Time interval from onset to DMT initiation, years*	2.17 ± 3.15
Number of relapses within 2 years after initial DMT[a]*	0.52 ± 0.93

Abbreviations: ARR, annualized relapse rate; CSF, cerebrospinal fluid; DMT, disease modifying treatment; IEF, isoelectric focusing; IFNb, interferon beta; IgG, immunoglobulin G; OCB, oligoclonal band; SD, standard deviation.
[a] For 184 out of 266 patients who were treated for at least 2 years.
[b] For 97 patients who have relapsed despite DMT.
[c] For 164 patients who had available baseline MRI.
[d] Only OCB by Isoelectric focussing was assessed
* Expressed as mean ± SD.

significantly higher in patients born 1986 or later compared to those born between 1970 and 1985. It was also higher in patients with a disease onset between 2006 and 2010 compared to those with a disease onset in 2005 and earlier (Fig. 3).

3.5. Prognosis

We assessed whether the year of birth and/or the year of disease onset were associated with the prognosis of our patients. In all patients with any DMT, both the age at initiation of the first DMT and the year of birth were associated with a risk of relapse after the first DMT. Nevertheless, in a subgroup analysis for patients with their first line DMTs of a similar efficacy in ARR reduction (between 33% and 36%) (Fogarty et al., 2016), only a younger age at initiation of the first DMT was associated with a higher risk of relapse after first line DMT (Table 4).

The time to confirmed EDSS 6 was only associated with the age at onset (HR = 2.137 for 10 years of increasing age; CI = 1.003–4.554; p = 0.049). Neither the year of birth nor the year of disease onset was associated with the time to confirmed EDSS 4 or 6, respectively (Supplementary table).

Fig. 1. Association between baseline brain MRI T2 lesion numbers and the year of birth.
The number of baseline brain MRI T2 lesions is increased by 1.288 per 10 year increase in the year of birth.

3.6. Earlier treatment in patients with more recent year of birth and/or disease onset

We also assessed the association between the year of birth and/or year of disease onset with the time from disease onset to initiation of the DMT. Both the birth year and the year of disease onset were associated with the time from disease onset to the initiation of DMT (Fig. 4).

4. Discussion

Our study showed that the year of birth was positively associated with the number of baseline T2 MRI lesions and positivity of OCB by IEF in adult-onset Korean MS. The ratio of female MS patients to males also showed an increasing trend. Nevertheless, neither the birth year nor the year of disease onset was associated with the outcomes of our MS patients, which may be attributed to the earlier treatment patterns in patients with more recent year of birth and/or disease onset.

Both the genetic susceptibility and environmental factors can play a crucial role in developing MS (Olsson et al., 2017). Considering the extremely low ethnic diversity and low number of immigrants in Korea (Fearon, 2003), it seems unlikely that the genetic susceptibility could change the patterns of MS in Korea. Rather, recent epidemiologic studies in Korea have shown an increasing rate of adolescent obesity (Ha and Kim, 2016), a high prevalence of vitamin D insufficiency in young age group (Choi et al., 2011), a high percentage of shift work including night work (Kwon et al., 2016), and rapid urbanization (Kim and Kim, 2011). As all of these factors have been proposed as either confirmed or potential risk factors for MS (Kotzamani et al., 2012; Langer-Gould et al., 2013; Mowry et al., 2012; Munger et al., 2013, 2009), it is reasonable to assume that the changing patterns of Korean MS in our study could be attributable to the recent rapid nationwide environmental changes. Our findings are in accordance with

Table 2
Univariate Poisson regression analysis of factors influencing baseline MRI T2 lesion numbers.

	Univariate analysis RR (95% CI)	p-value
Year of birth, (per 10 years)	1.266 (1.209 - 1.325)[a]	<0.001
Female sex (ref = male)	1.130 (1.040-1.228)[b]	0.004
Time from disease onset to baseline MRI (per month)	1.027 (1.004-1.050)[c]	0.023
Year of disease onset (per month)	1.219 (1.098-1.353)[b]	<0.001
Year of baseline MRI taken (per 10 years)	1.288 (1.153 - 1.439) [b]	<0.001

Abbreviations: RR = relative ratio, CI = confidence interval.

Table 3
Two models of multivariate Poisson analysis for factors associated with baseline MRI T2 lesion numbers.

	RR (95% CI)	*p*-value
Model 1		
Year of birth (per 10 years)	1.268 (1.221-1.317)[b]	<0.001
Female sex (ref=male)	1.130 (1.062-1.202)[c]	<0.001
Time from disease onset to baseline MRI (per month)	1.088 (1.074-1.102)[d]	<0.001
Year of disease onset (per 10 years)	1.064 (0.984-1.151)[b]	0.121
Model 2		
Year of birth (per 10 years)	1.279 (1.217 - 1.344)[a]	<0.001
Female sex (ref=male)	1.122 (1.031-1.220)[b]	0.007
Time from disease onset to baseline MRI (per month)	1.056 (1.031-1.081)[c]	<0.001
Year of baseline MRI taken (per 10 years)	1.030 (0.915 - 1.160) [a]	0.626

Abbreviations: RR = relative ratio, CI = confidence interval.

recent immigration studies of MS demonstrating that the severity as well as the prevalence of MS were increased in immigrants from low MS-risk (Browne et al., 2014) to high MS-risk countries (Ahlgren et al., 2010, 2012; Guimond et al., 2014; Smestad et al., 2008).

The prevalence of female MS patients is increasing globally (Koch-Henriksen and Sørensen, 2010) and a recent study proposed that a rapid transition from rural to urban life could be associated with this phenomenon (Kotzamani et al., 2012). Similarly, the rate of the Korean population living in metropolitan areas has risen to 49.5% in 2017 compared to approximately 20% in the 1950s (KOSTAT, 2017). We speculate that this rapid urbanization in Korea could be another major environmental change that may be associated with the increase in female MS in Korea.

The overall clinical patterns of MS in Asian countries are considered to be comparable with those in Western countries (Kim and Kim, 2016). Nevertheless, previous studies has shown that the Asian MS patients could have less disseminated baseline MRI lesions (Lo et al., 2009), low intrathecal OCB positivity rate (Kikuchi et al., 2003; Kim et al., 2013), and a relatively mild disease course (Kim et al., 2013; Piccolo et al., 2015). Therefore, our findings of more baseline T2 MRI lesions and higher OCB positive rate in a more recently born Korean MS patients, might imply that the pattern of Asian or Korean MS may be changing toward a more Westernized patterns.

The baseline MRI T2 lesion burden has been consistently reported to be a strong prognostic factor for worse outcomes among patients with MS (Fisniku et al., 2008; Tintoré et al., 2006). Moreover, recent large meta-analyses showed that OCB positivity can be a risk factor for disease progression in MS (Dobson et al., 2013). Nevertheless, despite the fact that the birth year was positively associated with both the baseline MRI T2 lesions and the OCB positivity, it was not associated with the prognosis of patients in terms of relapse risks or disease progression. We speculate that this could be due to the earlier treatment patterns in patients more recently born, as was shown in our data. Our another findings, that younger age was associated with more frequent relapses but less disease progression, were also in accordance with previous findings based on Western MS patients (Gorman et al., 2009; Harding et al., 2013).

The differential diagnosis of MS from NMOSD can be important for studies on MS in Asian region, as the relative frequency of NMO to MS (NMO/MS ratio) was high in cohort studies from this area; 1.06 in Korea (Kim et al., 2014) and 1.4 in Thailand (Siritho et al., 2011). In our 266 MS patients, 246 tested negative for AQP4-IgG assay and the other 20 patients did not meet the 2015 International Panel for NMO Diagnostic (IPND) criteria of NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status (Wingerchuk et al., 2015). Therefore none of our MS patients met the diagnostic criteria for NMOSD.

Our study has several limitations. First, despite the fact that this study was performed in a nation-wide multicenter cohort of 17 hospitals in Korea, the number of patients was relatively small, which was most attributable to the low prevalence of MS in Korea (Kim et al., 2010). Second, though 10 centers, participated in this study, included all of their MS patients (n = 225 patients, average 22.5 patients per center), the other 7 centers could only include consecutive MS patients (n = 41) that were seen in a given period (inclusion period varied according to centers). As we have included all or consecutive patients, we speculated that the risk of selection bias in our study seem to be relatively low. Nevertheless, we could have drawn more confirmatory results with a more number of patients that were thoroughly included all the MS patients from these 17 centers. Third, we have only included adult-onset MS patients in our study as we believe that the prognosis of

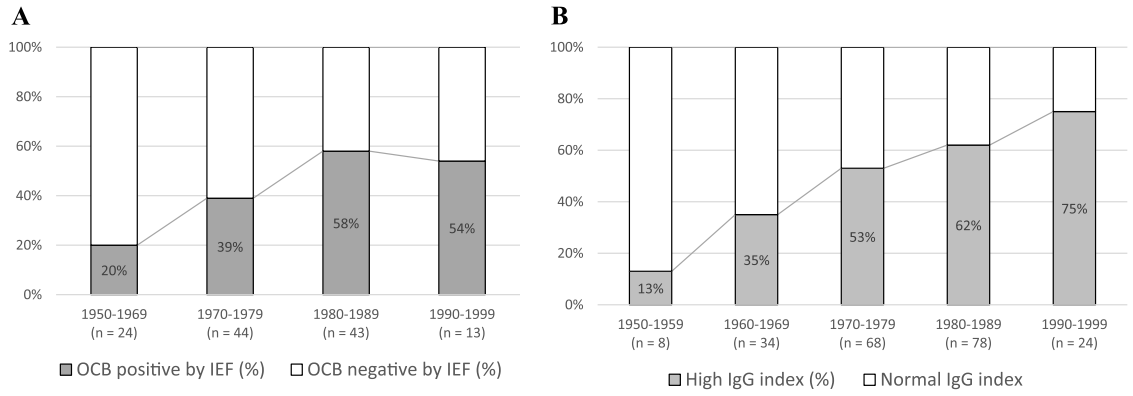

Fig. 2. Proportion of patients with positive CSF OCB by IEF and high IgG index according to the year of birth.
Among patients who underwent OCB testing by IEF (n = 125), the OCB positivity is higher in patients born in more recent years (OR = 1.723 per 10-year, 95% CI: 1.113–2.621, p = 0.011) (A). Patients born in more recent years also have a higher tendency to have a high IgG index (OR = 1.743 per 10-year, 95% CI: 1.1289–2.363, p < 0.001) (B).
Abbreviations: CI = confidence interval, OCB = oligoclonal band, OR = odd ratio, IEF = isoelectric focusing.

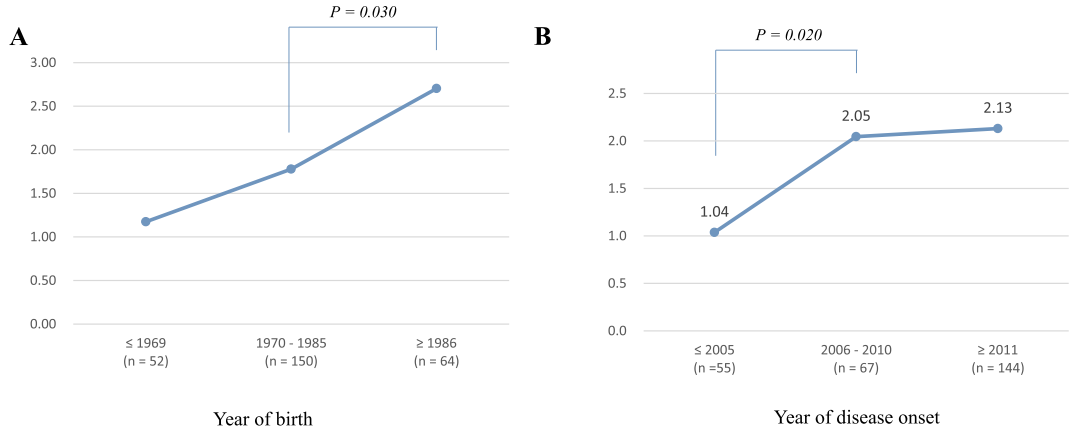

Fig. 3. Female to male ratio according to the year of birth and disease onset.
The female to male ratio is increased among patients born in 1985 or later compared to those between 1970 and 1985 (A). It is also increased among patients whose disease onset was between 2006 and 2010 compared to those with a disease onset in 2005 or earlier (B).

Table 4
Cox proportional hazards regression analysis to determine predictors for relapse risk despite first line disease modifying therapy.

	HR per 10 years (95% CI)	*p*-value
All patients with any DMT* (n = 236)		
Age at initiation of the first DMT	0.683 (0.537 - 0.869)	0.002
Year of birth	1.288 (1.032 – 1.607)	0.025
Year of disease onset	0.788 (0.506 - 1.226)	0.291
Time interval from disease onset to start of DMT	0.965 (0.892 - 1.045)	0.384
Patients with first line DMTs* (n = 216)		
Age at initiation of the first DMT	0.683 (0.531 - 0.879)	0.003
Year of birth	1.248 (0.991 - 1.571)	0.06
Year of disease onset	0.752 (0.477 - 1.186)	0.22
Time interval from disease onset to start of DMT	0.940 (0.860 - 1.027)	0.17

Abbreviations: HR, hazard ration; CI, confidence interval; DMT, disease modifying therapy.

* DMTs with ARR reduction rate between 33% – 36% were included.

pediatric MS might be different from adult-onset (Gorman et al., 2009; Harding et al., 2013). Fourth, we have validated the reliability of our data based on the number of baseline T2 lesions by intraclass correlation analysis, nevertheless we cannot completely rule out the possibility that the diversity of MRI machines and protocols could have affected our results. However, as we have shown that the baseline MRI T2 lesion was not associated with the year when the baseline MRI was taken, it does not appear that the development in MRI technique is responsible for our findings.

In conclusion, the disease pattern of adult-onset MS in Korea may be changing toward a more baseline MRI lesions, intrathecal humoral immune response, and a higher ratio of females. Further long term study with a larger number of patients seem to be needed to clarify the effect of these findings on their prognosis.

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Declaration of Competing Interest

H.-J. Shin, M.S. Park, E.H. Sohn, S.-H. Baek, Byung-Jo Kim, K. Choi, J. Oh, J.-Y. Cho, O. Kwon, W. Kim, J.E. Kim, J.-H. Min, Byoung Joon Kim, S.-Y. Oh, J.S. Bae, K.H. Park, J.-H. Oh, S.-Y. Sohn, and M.-J. Jang have nothing to disclose. J.-W. Hyun has received a grant from the National Research Foundation of Korea. S.-H. Kim has lectured, consulted, and received honoraria from Bayer Schering Pharma, Biogen, Genzyme, Merck Serono, and UCB and received a grant from the National Research Foundation of Korea. S.-M. Kim has lectured, consulted, and received honoraria from Bayer Schering Pharma, Genzyme, Merck Serono, and UCB; received a grant from the National Research

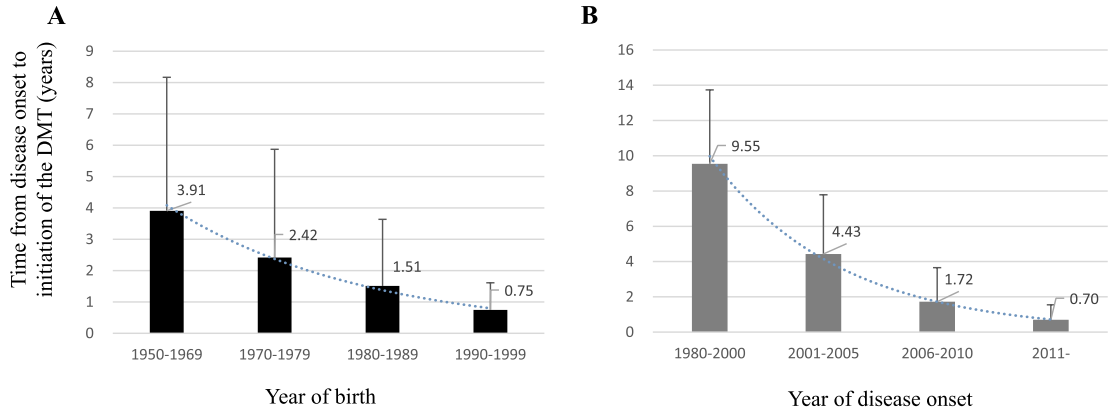

Figure 4. Trend toward early treatment.
The time from disease onset to initiate DMT is significantly decreased among those with a later year of birth (OR = −0.307 for increasing 10 years; CI = −1.433 to −0.641; $p < 0.001$) (A) and year of disease onset (OR = −0.695 for increasing 10 years; 95% CI = −4.215 to −3.269; $p < 0.001$) (B).

Foundation of Korea and the Korea Health Industry Development Institute Research; is an Associated Editor of the *Journal of Clinical Neurology*; S-M. Kim and Seoul National University Hospital has transferred the technology of flow cytometric AQP4-Ab assay to EONE Laboratory, Korea. H.J. Kim has lectured, consulted, and received honoraria from Bayer Schering Pharma, Biogen, Genzyme, HanAll BioPharma, MedImmune, Merck Serono, Novartis, Teva-Handok, and UCB; received a grant from the Ministry of Science, ICT & Future Planning; and accepted research funding from Genzyme, Kael-GemVax, Merck Serono, 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*.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.08.004.

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