Multiple sclerosis in Japan: Nationwide surveys over 30 years

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Abstract

There are two different phenotypes of multiple sclerosis (MS) in Asians: opticospinal (OSMS) and conventional (CMS). In Japan, four nationwide surveys of MS have been performed. The first three were in 1972, 1982 and 1989, and we conducted the fourth in 2004. Based on clinically estimated sites of lesions, 1,493 patients with clinically definite MS were classified as having CMS (57.7%), optic-brainstem-spinal MS (5.8%), brainstem-spinal MS (4.6%), OSMS (16.5%), spinal MS (10.6%) or unclassified MS (4.9%). The latest survey revealed the following: a four-fold increase in the estimated number of clinically definite MS patients in 2003 (9,900; crude MS prevalence, 7.7/100,000) compared with 1972; a shift in the peak age at onset from the early 30s in 1989 to the early 20s in 2003; a successive proportional decrease in optic-spinal involvement in clinically definite MS patients; a significant north-south gradient for the CMS/OSMS ratio; after subdivision of the mainland (30-45° North) into northern and southern parts at 37°N, northern-born northern-residents showed a significantly higher CMS/OSMS ratio and higher frequency of brain lesions fulfilling the Barkhof criteria (Barkhof brain lesions) than southern-born southern-residents; among northern patients, the absolute numbers of CMS patients and those with Barkhof brain lesions rapidly increased with advancing birth year. Based on MRI findings, MS patients were further subdivided into those with OSMS with or without longitudinally extensive spinal cord lesions extending over three or more vertebral segments (LESCLs) and those with CMS with or without LESCLs. Although disease duration did not differ significantly among the four groups, EDSS scores were significantly higher in patients with LESCLs than in those without, irrespective of OSMS or CMS phenotype. Similar trends were found for the frequencies of bilateral visual loss, transverse myelitis, and marked CSF pleocytosis and neutrophilia. Increased IgG index, frequencies of brain lesions fulfilling the Barkhof criteria and secondary progression were more commonly found in CMS patients than in OSMS patients, while negative brain MRIs were more commonly encountered in OSMS patients than CMS patients, irrespective of the presence of LESCLs. These findings suggest that MS phenotypes are drastically changed by environmental factors, such as latitude and "Westernization", and that demographic features not only vary based on CMS or OSMS phenotype, but also with the presence or absence of LESCLs.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) caused by a complex interplay between genetic and environmental factors. Although MS is rare in Asians, selective and severe involvement of the optic nerve and spinal cord is characteristic.[1] Okinaka *et al*[2] first reported a large series of Japanese patients with demyelinating diseases in 1958, among whom 175 of 270 cases were described as having Devic's neuromyelitis optica (NMO), and classical MS was rare. Because these authors found many intermediate cases between NMO and classical MS[2], only monophasic NMO has been referred to as NMO, while relapsing NMO is included within the spectrum of MS.[3] In Japan, the latter group has been designated as having the opticospinal form of MS (OSMS) and its clinical criteria was proposed in 1996.[4] Recently, NMO-IgG, a newly identified marker for NMO[5], was also detected in a fraction of Japanese OSMS patients[6,7], and OSMS is now postulated to be the same disease as relapsing NMO.[8] However, it remains to be elucidated whether MS, OSMS and NMO are distinct diseases or if they form

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a continuum.[7-10] Japanese are suitable for investigating phenotypic alterations over time in genetically homogeneous and geographically isolated populations who have experienced rapid environmental changes. Because nationwide surveys of MS in Japan were performed using essentially identical criteria in 1972, 1982 and 1989[11-12], we conducted a fourth nationwide survey in 2004 to uncover any phenotypic alterations in MS that have occurred during Japan's period of rapid "Westernization".[13]

SURVEY PROCEDURES

The fourth nationwide survey of MS was conducted by the Research Committees of Neuroimmunological Diseases and of Epidemiology of Intractable Diseases, funded by the Ministry of Health, Labour and Welfare, Japan. The survey was undertaken in two steps: first, a preliminary survey to ascertain the approximate number of MS patients in Japan, and second, a survey using a questionnaire sheet for each patient. The questionnaire for the preliminary survey on MS patients who visited hospitals due to disease within the period from 1 January to 31 December 2003 was mailed to 6,708 departments (comprising 1,933 neurology/internal medicine, 1,227 orthopaedics, 997 psychiatry, 945 paediatrics, 831 ophthalmology, 759 neurosurgery and 16 rehabilitation departments) together with the diagnostic criteria in January 2004. Following the collection and collation of the first questionnaire, a second questionnaire was forwarded to those institutions reporting patients in the first survey. The second questionnaire requested detailed clinical information on individual patients, including their ages at onset and examination, sex, birthplace, present address, symptoms based on history and signs from physical examination, laboratory findings, course, treatment and prognosis.

The diagnostic criteria used for the present survey were based on those used for the first nationwide survey in 1972[11], except that the limitation of age at onset was removed, as it was in the third survey.[12] The criteria required multiplicity in time and space and were essentially the same as Schumacher's criteria.[14] Patients with clinically definite MS fulfilled all of the criteria, while a diagnosis of possible MS was made when all three criteria for clinically definite MS could not be fulfilled, but the signs were suggestive. The criteria for primary progressive MS (PPMS) were taken from McDonald's criteria.[15] Data from cases

with monophasic NMO were also collected. The criteria for monophasic NMO were as follows: acute bilateral visual impairment (optic neuritis) and transverse myelitis occurring successively within several weeks.

The classification of MS subtypes was based on clinically estimated sites of lesions. The second questionnaire requested the respondents to mark the clinically estimated sites of the lesions according to the symptomatology during the entire clinical course among the following sites: optic nerve, cerebrum, cerebellum, brainstem and spinal cord. The survey centre classified each case into the following clinical subtypes based on the clinically estimated lesion sites reported by each institution: OSMS involving the optic nerve and the spinal cord, optic-brainstem-spinal MS (OBSMS) involving the optic nerve, brainstem and spinal cord, brainstem-spinal MS (BSMS) involving the brainstem and the spinal cord, spinal MS (SMS) involving only the spinal cord, which was identical to recurrent myelitis without any known cause, and conventional MS (CMS), which involved multiple sites of the CNS, including the cerebrum and/or cerebellum.

COMPARISON WITH PREVIOUS SURVEY RESULTS

In the preliminary survey, 3,749 institutions (55.9%) reported 4,827 MS patients, including 849 patients with possible MS. In the second questionnaire, detailed data were collected for 1,919 patients (39.3% of the preliminary survey), including 30 duplicate cases. Thus the estimated number of clinically definite MS patients in 2003 was 9,900 (95% CI: 9,100-10,700), representing a four-fold increase compared with the first nationwide survey in 1972 (Table 1).[11] The estimated crude prevalence was 7.7/100,000 (95% CI: 7.1-8.4). The proportions of patients with clinically definite MS and female patients had increased since the first survey. The percentage of patients with monophasic NMO among all MS patients as well as the absolute number of patients with this subtype had progressively decreased over time. Compared with the third nationwide survey, the peak age at onset had decreased and the second peak in the early 50s had disappeared (Fig. 1A). Visual loss at onset and during the entire clinical course, and optic atrophy during the entire course, had decreased over the period of the four surveys.

Table 1: Comparison of demographic features among the four nationwide survey

Year of survey	1972	1982	1989	2004[a]
Estimated number of clinically definite MS patients	2,280	N.D.	3,700	9,900
Number of cases collated for the final survey	1,084	1,518	1,270	1,889
Sex ratio (male : female)	1 : 1.7	1 : 2.3	1 : 2.6	1 : 2.9
Clinically definite MS (%)[b]	46.9	55.9	67.8	84.5
Monophasic NMO (%)[b]	7.6	5.1	3.6	1.2
Age at onset (mean ± SD, years)[b]	33 ± 13	32 ± 13	34 ± 13	32 ± 13
Age at examination (mean ± SD, years)[b]	39 ± 13	40 ± 13	41 ± 14	42 ± 14
Mean disease duration (years)[b]	6	8	8	10
Visual loss at onset (%)	41.8	34.6	36.6	29.5
Visual loss during entire course (%)	79	N.D.	70.4	56.1
Optic atrophy during entire course (%)	62	N.D.	52.2	32.3
Quadriparesis during entire course (%)	N.D.	N.D.	38.3	18.4
Transverse myelitis during entire course (%)	N.D.	N.D.	36.7	27.4

MS = multiple sclerosis; N.D. = not determined; NMO = neuromyelitis optica.
[a]Interferon beta-1b, the only disease-modifying drug available in Japan since 2001, was administered in 37.2% of the cases in 2003.
[b]Data from all MS patients including possible MS and monophasic NMO are shown. When the small numbers of primary progressive MS patients (n = 40) in the present survey were omitted, all statistical analyses in the following sections gave essentially the same results.

CLINICAL FEATURES

According to the clinically estimated sites of lesions, 1,493 patients with clinically definite MS were classified into CMS (57.7%), OBSMS (5.8%), BSMS (4.6%), OSMS (16.5%), SMS (10.6%) or unclassified MS (4.9%). There were no significant differences in disease durations among the subtypes other than a significantly shorter disease duration in SMS patients compared with CMS and OSMS patients. Comparisons of the clinical features between CMS and OSMS patients revealed significant differences in many aspects (Table 2). Compared with CMS patients, OSMS patients showed a significantly higher age at onset, greater proportion of females, higher expanded disability status scale (EDSS) of Kurtzke score[16], and higher frequencies of bilateral visual loss, transverse myelitis, paraparesis, sensory impairment below a certain level and sphincter disturbance. By contrast, OSMS patients had significantly lower frequencies of secondary progression and increased IgG index in the cerebrospinal fluid (CSF) than CMS patients. The occurrences of brain lesions fulfilling the Barkhof criteria[17] (Barkhof brain lesions) and each item of the criteria were significantly higher in CMS patients than in OSMS patients (P < 0.001), while longitudinally extensive spinal cord lesions (LESCLs) extending over three or more vertebral segments and gadolinium-enhanced spinal cord lesions showed the reverse trend (P < 0.001).

DIFFERENCES IN CLINICAL PHENOTYPES BY LATITUDE AND BIRTH YEAR

A significant negative correlation was found between the proportion of patients with OSMS and the northern latitude of present residence (r = -0.31, P = 0.04). When the mainland (30-45° North) was subdivided into northern and southern parts at 37° North, northern-born northern-residents (northern patients) showed a significantly higher CMS/OSMS ratio than southern-born southern-residents (southern patients). Migrants, especially northern-born southern-residents, showed intermediate CMS/OSMS ratios between those of the northern and southern patients (Fig. 2A). The CMS/OSMS ratio increased dramatically with advancing year of birth among northern patients, but such a trend was modest among southern patients (Fig. 3A, B). There was a steady increase in the absolute numbers of CMS patients among both northern and southern patients with advancing year of birth.
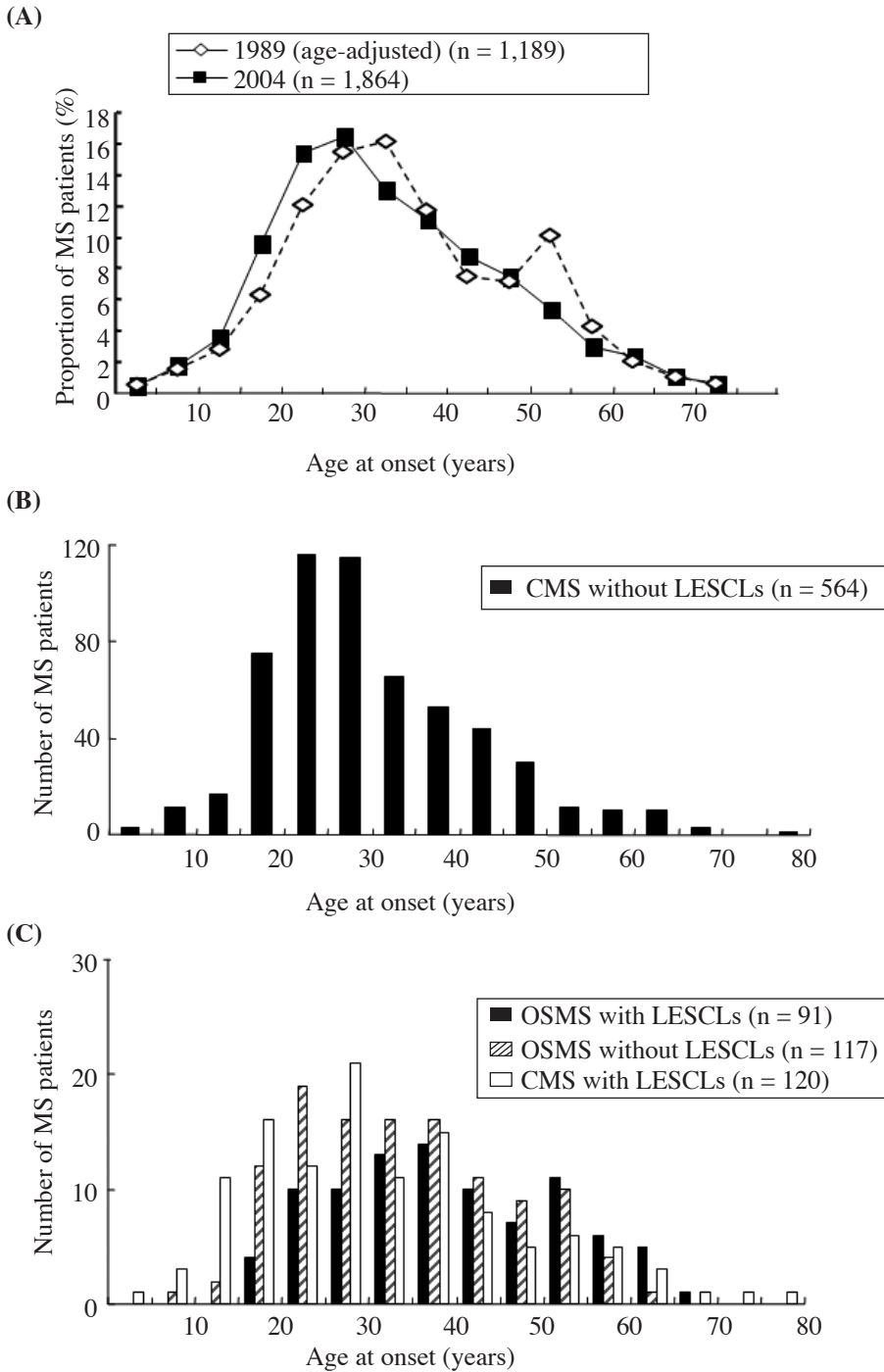
(A)

(B)

(C)

Fig. 1 Distribution of ages at onset in all patients with clinically definite MS (**A**). Distribution of age at onset in patients with conventional multiple sclerosis (CMS) without longitudinal extensive spinal cord lesions (LESCLs) (**B**), CMS without LESCLs, opticospinal multiple sclerosis (OSMS) patients with LESCLs and OSMS patients without LESCLs (**C**).

In (**A**), the proportions of MS patients at each age at onset in 1989 have been adjusted to the age distribution of the Japanese population in 2003. Note that the age at onset curve shifts toward the younger side in 2004, while the second peak around the early 50s seen in 1989 is no longer evident. In (**B**) and (**C**), "anticipation" of age at onset is more pronounced in patients without LESCLs, irrespective of CMS or OSMS phenotype. The second peak around the early 50s is not evident in CMS patients without LESCLs, but is still identifiable in the other three subtypes.

Table 2: Clinical characteristics among each multiple selerosis subgroup classified according to the clinically estimated sites of the lesions

	OSMS (n = 246)	CMS (n = 862)	P value
Sex ratio (male:female)	1:4.5	1:2.4	< 0.001
Age at onset (years)	35.4 ± 12.9	29.3 ± 12.5	< 0.001
Age at examination (years)	47.1 ± 14.1	39.9 ± 13.6	< 0.001
Disease duration (years)	11.7 ± 9.1	10.6 ± 8.4	N.S.
EDSS scores	4.3 ± 2.7	3.5 ± 2.9	< 0.001
Symptoms during entire course			
Bilateral visual loss	131/246 (53.3%)	260/851 (30.6%)	< 0.001
Transverse myelitis	113/231 (48.9%)	170/823 (20.7%)	< 0.001
Paraparesis	139/239 (58.2%)	319/839 (38.0%)	< 0.001
Quadriparesis	46/238 (19.3%)	160/848 (18.9%)	N.S.
Sensory impairment below a certain level	141/224 (62.9%)	223/777 (28.7%)	< 0.001
Sphincter disturbance	155/238 (65.1%)	393/848 (46.3%)	< 0.001
Severe motor disability at the time of last examination[#]	57/231 (24.7%)	142/805 (17.6%)	0.017
Secondary progression	19/246 (7.7%)	131/861 (15.2%)	0.003
Cerebrospinal fluid findings			
Marked pleocytosis ($\geq$ 50 W BC/mm^3) or neutrophilia ($\geq$ 5 neutrophils/mm^3)	21/191 (11.0%)	51/730 (7.0%)	N.S.
Increase IgG index	31/106 (29.2%)	240/397 (60.5%)	< 0.001
Brain MRI findings			
$\geq$ 1 Gd-enhanced lesion or $\geq$ 9 T2 brain lesions	41/226 (18.1%)	507/840 (60.4%)	< 0.001
$\geq$ 9 T2 brain lesions	37/226 (16.4%)	390/840 (46.4%)	< 0.001
$\geq$ 1 Gd-enhanced lesion	10/199 (5.0%)	292/688 (42.4%)	< 0.001
$\geq$ 1 Juxtacortical lesion	28/218 (12.8%)	303/786 (38.5%)	< 0.001
$\geq$ 3 Periventricular lesions	59/221 (26.7%)	526/806 (65.3%)	< 0.001
$\geq$ 1 Infratentorial lesion	42/219 (19.2%)	539/827 (65.2%)	< 0.001
Lesions fulfilling the Barkhof criteria	19/223 (8.5%)	382/844 (45.3%)	< 0.001
No cranial lesion	94/223 (42.2%)	16/844 (1.9%)	< 0.001
Spinal cord MRI findings			
$\geq$ 1 T2 lesion	203/223 (91.0%)	508/724 (70.2%)	< 0.001
LESCL	93/223 (41.7%)	121/724 (16.7%)	< 0.001
Gd-enhanced lesion	99/181 (54.7%)	187/653 (28.6%)	< 0.001

#: Chair-bound or worse. CMS = conventional form of multiple sclerosis; EDSS = expandad disability status scale of Kurtzke; Gd = gadolinium; LESCLs = longitudinally extensive spinal cord lesions extending 3 or more vertebral segments; N.S. = not significant; OSMS = opticospinal form of multiple sclerosis.

DIFFERENCES IN MRI FINDINGS BY LATITUDE AND BIRTH YEAR

Among the CMS patients, northern patients demonstrated a significantly higher frequency of Barkhof brain lesions than southern patients (P < 0.001) and northern-born southern-residents (P = 0.02) (Fig. 2B), whereas southern patients had significantly more LESCLs than northern patients (P < 0.001) (Fig. 2C). Among MS patients, the proportions and absolute numbers of patients with Barkhof brain lesions steadily increased with advancing year of birth among both northern and southern patients, but the trend was far more marked in northern patients (Fig. 4A, B). The same was true for CMS patients (Fig. 4C, D). Among
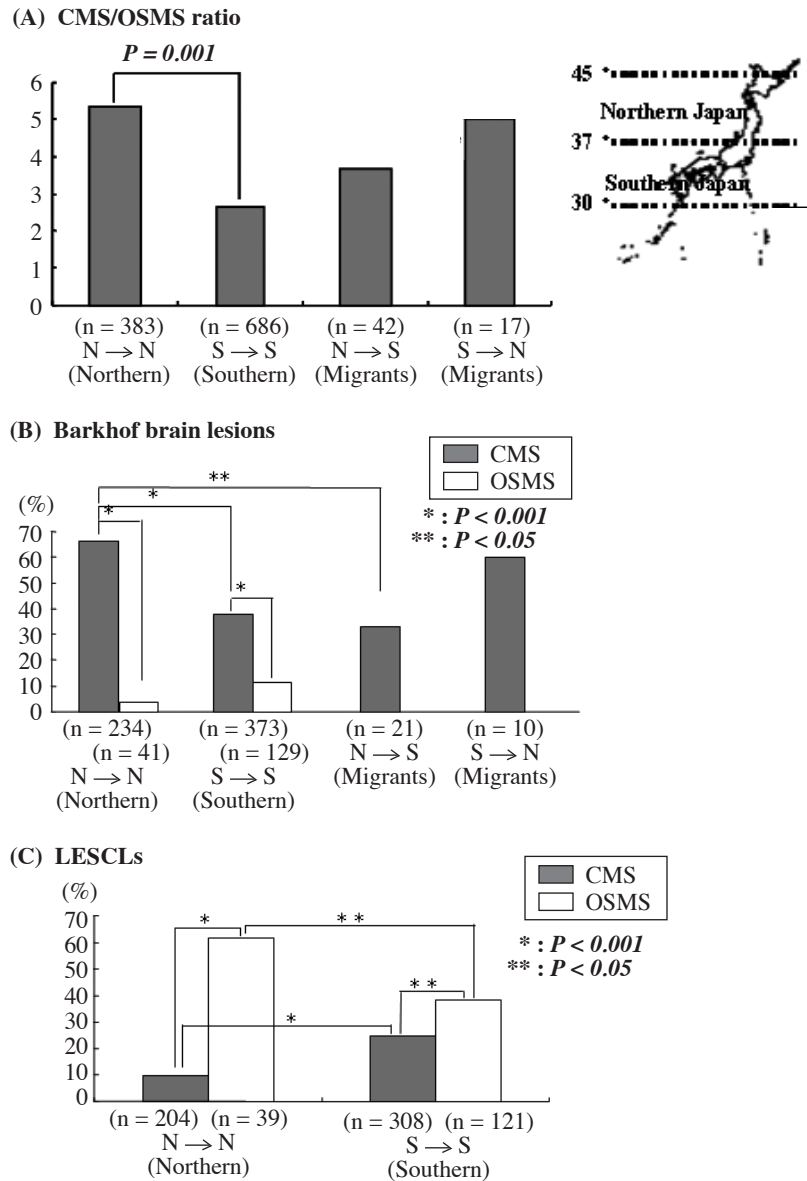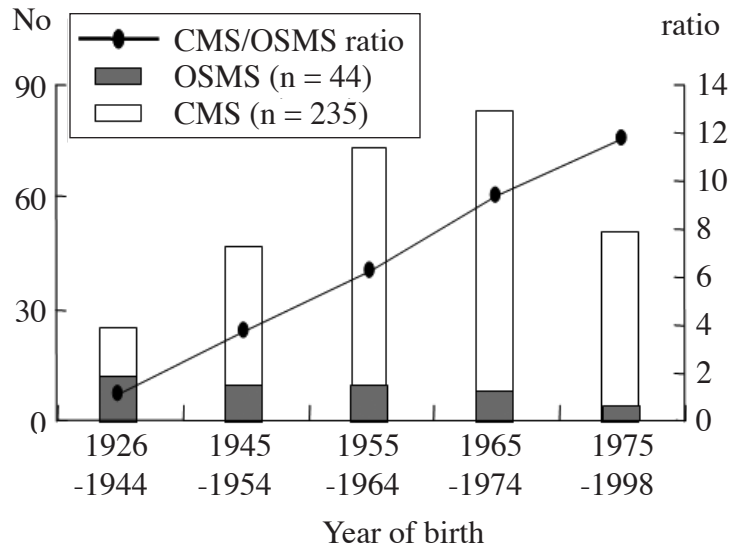
(A) CMS/OSMS ratio

P = 0.001

(B) Barkhof brain lesions

* : P < 0.001
** : P < 0.05

(C) LESCLs

* : P < 0.001
** : P < 0.05

Fig. 2   Conventional multiple sclerosis/opticospinal multiple sclerosis (CMS/OSMS) ratios in relation to place of birth and residence (**A**). Frequencies of brain MRI lesions fulfilling the Barkhof criteria in relation to place of birth and residence (**B**). Frequencies of longitudinally extensive spinal cord lesions (LESCLs) on MRI (**C**) in northern-born northern-residents (N➤N) (northern patients), southern-born southern-residents (S ➤S) (southern patients), northern-born southern-residents (N➤S) and southern-born northern-residents (S➤N).

In (**A**), the Japanese mainland (inset in **A**), located from 30° North to 45° North, is arbitrarily divided into northern and southern parts at a latitude of 37° North. The respective CMS/OSMS ratios are shown for northern-born northern-residents (N➤N), southern-born southern-residents (S➤S), northern-born southern-residents (N➤S) and southern-born northern-residents (S➤N). The CMS/OSMS ratio is significantly higher in northern-born northern-residents (northern patients) than in southern-born southern-residents (southern patients) (*P* < 0.001). In (**B**), among patients with CMS, brain lesions fulfilling the Barkhof criteria are significantly more common in northern patients than in southern patients. Among CMS patients, the frequency of Barkhof brain lesions is significantly lower in northern-born southern-residents than in northern-born northern-residents. The frequencies of Barkhof brain lesions in the OSMS groups are not shown in migrants because the sample numbers were too small. In (**C**), the difference in the frequencies of LESCLs between OSMS and CMS patients is marked in northern patients, but rather small in southern patients.

(A) CMS/OSMS ratio in northern Japan

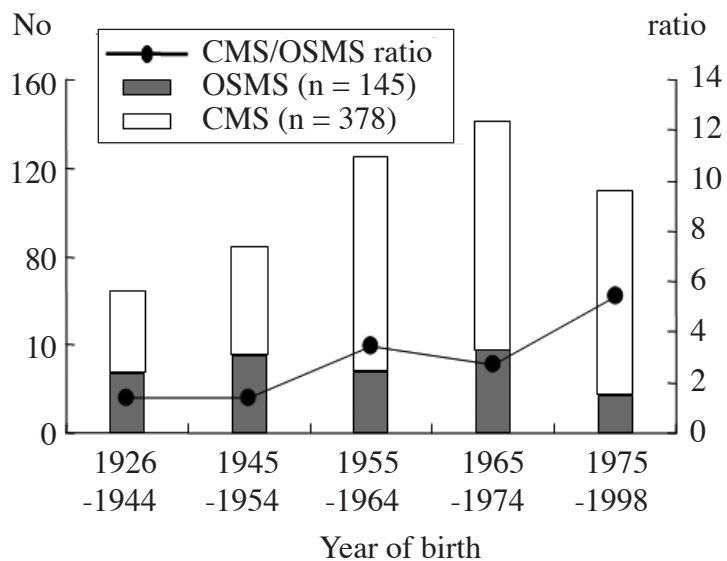
(B) CMS/OSMS ratio in southern Japan

Fig. 3 Changes in the clinical phenotypes of patients with clinically definite MS in relation to year of birth. Conventional multiple sclerosis/opticospinal multiple sclerosis (CMS/OSMS) ratios and absolute numbers of patients with each phenotype in relation to year of birth among northern (**A**) and southern (**B**) patients. In (**A**) and (**B**), the CMS/OSMS ratios are compared between northern and southern patients and configured according to the year of birth. The ratio steadily increases with advancing year of birth. Each bar indicates the absolute number in each group in the indicated birth years, while each dotted line shows the changes in the ratios or percentages.
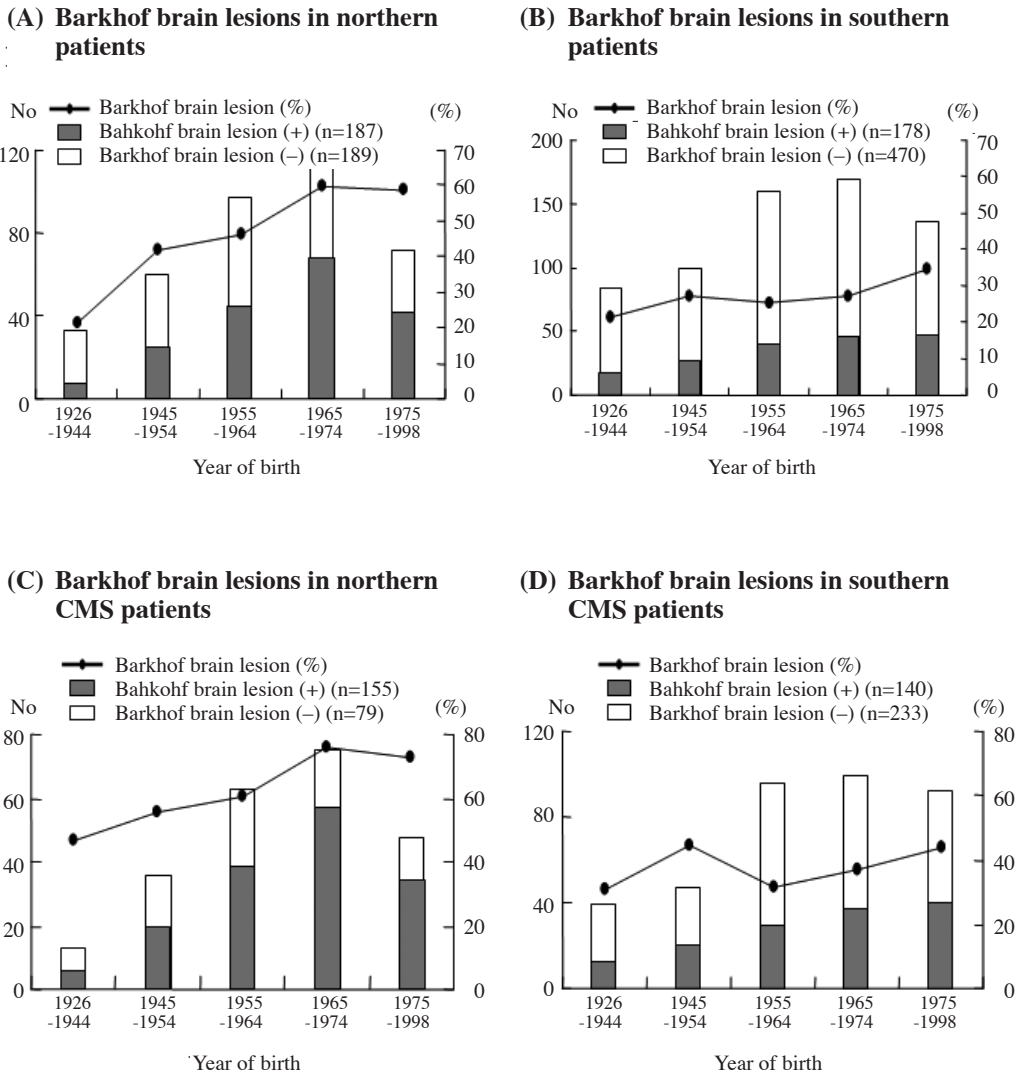
(A) Barkhof brain lesions in northern patients

(B) Barkhof brain lesions in southern patients

(C) Barkhof brain lesions in northern CMS patients

(D) Barkhof brain lesions in southern CMS patients

Fig. 4   Changes in the proportions and absolute numbers of patients with Barkhof brain lesions in relation to year of birth among northern (**A**) and southern (**B**) patients. Changes in the proportions and absolute numbers of conventional multiple sclerosis (CMS) patients with Barkhof brain lesions in relation to birth year among northern (**C**) and southern (**D**) patients.

In (**A**) and (**B**), the proportions and absolute numbers of patients with brain lesions fulfilling the Barkhof criteria are increased among northern patients with descending year of birth. Bars indicate the absolute numbers in each group with the indicated birth years, while dotted lines show the percentages of patients positive for Barkhof brain lesions in the indicated birth year in northern and southern MS patients. In (**C**) and (**D**), bars indicate the absolute number in each group with the indicated birth years, while dotted lines show the percentages of patients positive for Barkhof brain lesions in the indicated birth year in northern and southern CMS patients.
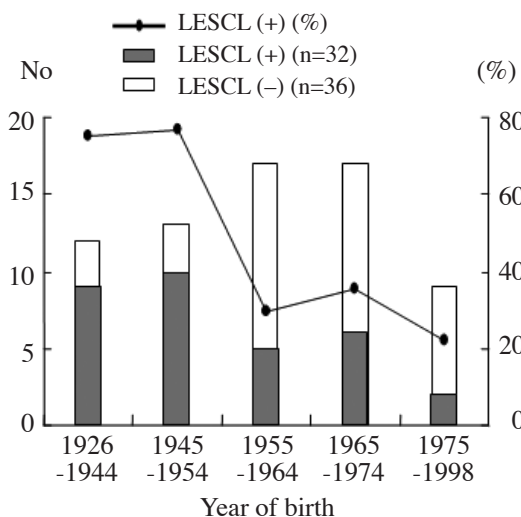
(A) LESCLs in northern patients
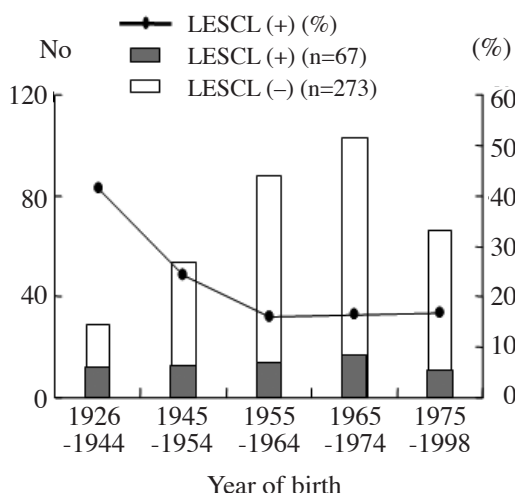
(B) LESCLs in southern patients
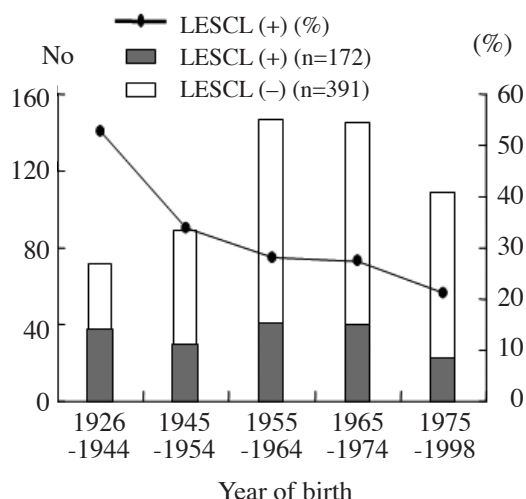
(C) LESCLs in northern OSMS+SMS patients
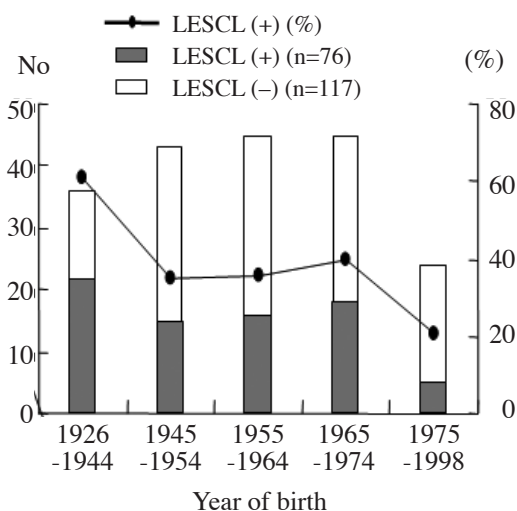
(D) LESCLs in southern OSMS+SMS patients

Fig. 5   Proportions and absolute numbers of patients with longitudinal extensive spinal cord lesions (LESCLs) in relation to year of birth among northern (**A**) and southern (**B**) patients. Changes in the proportions and absolute numbers of opticospinal multiple sclerosis and spinal multiple sclerosis (OSMS+SMS) patients with LESCLs in relation to birth year among northern (**C**) and southern (**D**) patients.
In (**A**) and (**B**), only the proportions of patients with LESCLs decreased with descending year of birth among both northern and southern patients. Bars indicate the absolute numbers in each group with the indicated birth years, while dotted lines show the percentages of patients positive for LESCLs in the indicated birth year in northern and southern MS patients. In (**C**) and (**D**), bars indicate the absolute number in each group with the indicated birth years, while dotted lines show the percentages of patients positive for LESCLs in the indicated birth year in northern and southern OSMS plus SMS patients.

Table 3: Multiple logistic analysis for possible factors contributing to the development of Barkhof brain lesions in patients with multiple sclerosis

	Odds ratio	95% CI	*P* value
CMS	5.389	(3.616 – 8.031)	< 0.0001
Female	0.784	(0.518 – 1.187)	0.2501
Age at onset (years)	0.990	(0.974 – 1.007)	0.2689
Disease duration (years)	1.019	(0.991 – 1.048)	0.1863
Northern residence	2.205	(1.513 – 3.214)	< 0.0001
EDSS score	1.090	(1.005 – 1.182)	0.0380
Increased CSF IgG index	1.678	(1.156 – 2.435)	0.0064
Marked CSF pleocytosis	0.097	(0.021 – 0.443)	0.0026

Clinically definite multiple sclerosis patients were divided into those with or without Barkhof brain lesions.
CI = confidential interval; CSF = cerebrospinal fluid; EDSS = expanded disability status scale of Kurtzke;
CMS = conventional form of multiple sclerosis.

Table 4: Multiple logistic analysis for possible factors contributing to the development of longitudinally extensive spinal cord lesions in patients with multiple sclerosis

	Odds ratio	95% CI	*P* value
OSMS	2.931	(1.578 – 5.444)	0.0007
Female	1.726	(0.949 – 3.137)	0.0735
Age at onset (years)	0.999	(0.977 – 1.022)	0.9399
Disease duration (years)	0.958	(0.922 – 0.995)	0.0284
Northern residence	0.723	(0.436 – 1.199)	0.2087
EDSS score	1.436	(1.282 – 1.608)	< 0.0001
Increased CSF IgG index	0.578	(0.343 – 0.975)	0.0398
Marked CSF pleocytosis	19.533	(3.475 – 109.798)	0.0007

Clinically definite multiple sclerosis patients were divided into those with or without LESCLs.
CI = confidential interval; CSF = cerebrospinal fluid; EDSS = expanded disability status scale of Kurtzke;
LESCLs = longitudinally extensive spinal cord lesions extending three or more vertebral segments;
OSMS = opticospinal form of multiple sclerosis.

MS patients, the proportions of patients with LESCLs successively decreased with advancing year of birth among both northern and southern patients, while the absolute numbers remained mostly unchanged over the wide range of birth years (Fig. 5A, B). The same was true for OSMS plus SMS patients (Fig. 5C, D).

MULTIPLE LOGISTIC ANALYSES

By multiple logistic analyses, CMS phenotype ($P < 0.0001$), northern residence ($P < 0.0001$), increased CSF IgG index ($P = 0.0064$) and EDSS score ($P = 0.0380$) were found to have significant positive associations with Barkhof brain lesions, while marked CSF pleocytosis was negatively associated with these measures ($P = 0.0026$) (Table 3). By contrast, EDSS score ($P < 0.0001$), marked CSF pleocytosis ($P = 0.0007$), OSMS ($P = 0.0007$) and disease duration ($P = 0.0284$) were positively associated with LESCLs, while increased IgG index was negatively associated ($P = 0.0398$) (Table 4).

Table 5: Clinical characteristics among each multiple selerosis subgroups

	OSMS		CMS	
	LESCL (+) (n = 93)	LESCL (–) (n = 117)	LESCL (+) (n = 121)	LESCL (–) (n = 570)
Sex ratio (male:female)	1:5.2[*k]	1:4.1	1:5.1[*h]	1:2.3[*h, *k]
Age at onset (years)	38.8 ± 12.8[*c, *e, *g]	33.2 ± 12.0[*d, *g]	31.1 ± 14.9[*c]	29.3 ± 11.9[*d, *e]
Age at examination (years)	49.8 ± 13.9[*c, *e, *g]	43.9 ± 13.2[*d, *g]	41.4 ± 15.6[*c]	39.7 ± 12.8[*d, *e]
Disease duration (years)	11.1 ± 8.0	10.6 ± 8.7	10.4 ± 8.8	10.4 ± 8.3
EDSS scores	5.4 ± 2.5[*a, *e]	3.2 ± 2.5[*a, *f]	4.9 ± 2.9[*b, *f]	3.2 ± 2.5[*b, *e]
Symptoms during entire course				
Bilateral visual loss	57/93 (61.3%)[*e]	51/117 (43.6%)[*d]	54/121 (44.6%)[*b]	142/563 (25.2%)[*b, *d, *e]
Transverse myelitis	58/91 (63.7%)[*a, *e]	39/113 (34.5%)[*a, *d]	57/116 (49.1%)[*b]	91/552 (16.5%)[*b, *d, *e]
Paraparesis	64/91 (70.3%)[*a, *e]	51/113 (45.1%)[*a]	67/116 (57.8%)[*b]	203/558 (36.4%)[*b, *e]
Quadriparesis	21/93 (22.6%)	18/112 (16.1%)[*l]	37/118 (31.4%)[*b, *l]	89/561 (15.9%)[*b]
Sensory impairment below a certain level	66/89 (74.2%)[*a, *e]	53/108 (49.1%)[*a, *d]	67/110 (60.9%)[*b]	130/528 (24.6%)[*b, *d, *e]
Sphincter disturbance	71/93 (76.3%)[*e]	61/114 (53.5%)[*a, *l]	86/120 (71.7%)[*b, *l]	251/563 (44.6%)[*b, *e]
Severe motor disability at the time of last examination[#]	30/89 (33.7%)[*g, *e]	18/110 (16.4%)[*g, *f]	43/116 (37.1%)[*b, *f]	70/534 (13.1%)[*b, *e]
Secondary progression	7/93 (7.5%)	6/117 (5.1%)[*l, *j]	22/121 (18.2%)[*l]	88/569 (15.5%)[*j]
Cerebrospinal fluid findings				
Marked pleocytosis (≥ 50 W BC/mm³) or neutrophilia (≥ 5 neutrophils/mm³)	16/79 (20.3%)[*a, *e]	3/96 (3.1%)[*a, *l]	17/102 (16.7%)[*b, *l]	21/511 (4.1%)[*b, *e]
Increase IgG index	12/45 (26.7%)[*e]	16/51 (31.4%)[*d]	29/59 (49.2%)	186/298 (62.4%)[*d, *e]
Brain MRI findings				
≥ 1 Gd-enhanced lesion or ≥ 9 T2 brain lesions	16/87 (18.4%)[*c, *e]	22/110 (20.0%)[*d, *f]	72/112 (64.3%)[*c, *f]	358/548 (65.3%)[*d, *e]
≥ 9 T2 brain lesions	13/87 (14.9%)[*c, *e]	21/110 (19.1%)[*d, *f]	49/112 (43.8%)[*c, *e]	281/547 (51.4%)[*d, *e]
≥ 1 Gd-enhanced lesion	5/79 (6.3%)[*c, *e]	5/99 (5.1%)[*d, *f]	43/100 (43.0%)[*c, *f]	210/481 (43.7%)[*d, *e]
≥ 1 Juxtacortical lesion	5/85 (5.9%)[*c, *e]	21/110 (19.1%)[*d, *f]	46/109 (42.2%)[*c, *f]	209/536 (39.0%)[*d, *e]
≥ 3 Periventricular lesions	21/86 (24.4%)[*c, *e]	34/111 (30.6%)[*d, *f]	69/114 (60.5%)[*c, *f]	365/546 (66.9%)[*d, *e]
≥ 1 Infratentorial lesion	11/87 (12.6%)[*c, *e]	26/107 (24.3%)[*d, *f]	69/116 (59.5%)[*c, *f]	372/559 (66.5%)[*d, *e]
Lesions fulfilling the Barkhof criteria	7/89 (7.9%)[*c, *e]	10/109 (9.2%)[*d, *f]	47/120 (39.2%)[*c, *f]	280/566 (49.5%)[*d, *e]
No cranial lesion	49/89 (55.1%)[*a, *c, *e]	39/109 (35.8%)[*a, *d, *f]	3/120 (2.5%)[*c, *f]	10/566 (1.8%)[*d, *e]
Spinal cord MRI findings				
≥ 1 T2 lesion	93/93 (100%)[*a, *e]	97/117 (82.9%)[*a, *d, *f]	121/121 (100%)[*b, *f]	354/570 (62.1%)[*b, *d, *e]
LESCL	93/93 (100%)[*a, *e]	0/117 (0%)[*a, *f]	121/121 (100%)[*b, *f]	0/570 (0%)[*b, *e]
Gd-enhanced lesion	59/75 (78.7%)[*a, *e]	39/99 (39.4%)[*a, *d, *f]	72/107 (67.3%)[*b, *f]	110/532 (20.7%)[*b, *d, *e]

#: Chair-bound or worse. CMS = conventional form of multiple sclerosis; EDSS = expandad disability status scale of Kurtzke; Gd = gadolinium; LESCLs = longitudinally extensive spinal cord lesions extending 3 or more vertebral segments; N.S. = not significant; OSMS = opticospinal form of multiple sclerosis.
*a : $P < 0.01$ (OSMS with LESCLs vs. OSMS without LESCLs), *b: $P < 0.001$ (CMS with LESCLs vs. CMS without LESCLs), *c: $P < 0.01$ (OSMS with LESCLs vs. CMS with LESCLs), *d: $P < 0.01$ (OSMS without LESCLs vs. CMS without LESCLs), *e: $P < 0.01$ (OSMS with LESCLs vs. CMS without LESCLs), *f: $P < 0.01$ (OSMS without LESCLs vs. CMS with LESCLs), *g: $0.01 \leq P < 0.05$ (OSMS with LESCLs vs. OSMS without LESCLs), *h: $0.01 \leq P < 0.05$ (CMS with LESCLs vs. CMS without LESCLs), *i: $0.01 \leq P < 0.05$ (OSMS with LESCLs vs. CMS with LESCLs), *j: $0.01 \leq P < 0.05$ (OSMS without LESCLs vs. CMS without LESCLs), *k: $0.01 \leq P < 0.05$ (OSMS with LESCLs vs. CMS without LESCLs), *l: $0.01 \leq P < 0.05$ (OSMS without LESCLs vs. CMS with LESCLs),

DEMOGRAPHIC FEATURES OF EACH MULTIPLE SCLEROSIS SUBTYPE

Based on the MRI findings, MS patients were subdivided into those with OSMS with or without LESCLs and those with CMS with or without LESCLs (Table 5). The proportion of females was significantly greater among OSMS or CMS patients with LESCLs than among CMS patients without LESCLs ($P^{corr} < 0.05$). Age at onset was significantly higher in OSMS patients with LESCLs than in other groups ($P^{corr} < 0.05$). The peak age at onset was early 20s among CMS or OSMS patients without LESCLs, late 20s among CMS patients with LESCLs, and late 30s among OSMS patients with LESCLs (Fig. 1B, C). Although disease duration did not differ significantly among the four groups, EDSS scores were significantly higher in patients with LESCLs than in those without LESCLs, irrespective of OSMS or CMS phenotype ($P^{corr} < 0.01$). Occurrences of bilateral visual loss, transverse myelitis, paraparesis, sensory level and sphincter disturbance were highest in OSMS patients with LESCLs among the four groups. CMS patients with LESCLs also showed a significantly higher frequency of these symptoms compared with CMS patients without LESCLs ($P^{corr} < 0.01$). Bilateral visual loss and transverse myelitis were significantly more common in OSMS patients without LESCLs than in CMS patients without LESCLs ($P^{corr} < 0.01$). Secondary progression was more common in CMS patients than OSMS patients, regardless of the presence or absence of LESCLs ($P^{corr} < 0.05$). In the CSF, marked pleocytosis or neutrophilia was more common in patients with LESCLs than in those without LESCLs, irrespective of a diagnosis of OSMS or CMS ($P^{corr} < 0.05$). Increased IgG index and brain lesions fulfilling the Barkhof criteria[17] were more commonly found in CMS patients than in OSMS patients, while negative brain MRIs were more commonly encountered in OSMS patients than CMS patients, irrespective of the presence of LESCLs ($P^{corr} < 0.01$). Gadolinium enhancement of the spinal cord lesions was significantly more common in patients with LESCLs than in those without, irrespective of clinical phenotype ($P^{corr} < 0.01$). These findings suggest that demographic features vary not only based on CMS or OSMS phenotype, but also with the presence or absence of LESCLs.

TEMPORAL CHANGES AND GEOGRAPHICAL DIFFERENCES OF CONVENTIONAL MULTIPLE SCLEROSIS

The fourth nationwide survey revealed, for the first time, that the increase in the prevalence of CMS differed with latitude, and that the emergence of MS-like brain lesions is also affected by latitude and year of birth. Geographically, the higher CMS/OSMS ratio and brain lesion loads in northern patients indicates the presence of environmental factors predisposing people in the north to Western-type MS. The results of multiple logistic analyses strongly support the presence of factors predisposing people in the north to the development of MS-like brain lesions. The reduction in the prevalence of the CMS phenotype and brain lesion burden owing to migration from north to south may indicate the existence of environmental factors predisposing people in the north to brain lesion development that operate continuously until early adulthood, or the existence of exogenous factors providing resistance to the CMS phenotype and brain lesion development in the south. Both the excess of CMS over OSMS and the increased number of patients with Barkhof brain MRI lesions with descending year of birth indicate phenotypic changes in MS associated with the year of birth. These findings point to a corresponding change in the distribution of environmental factors in Japan, especially in the north.

TEMPORAL CHANGES AND GEOGRAPHICAL DIFFERENCES OF NEUROMYELITIS OPTICA AND OPTICOSPINAL MULTIPLE SCLEROSIS

The four nationwide surveys disclosed a trend toward decreased proportions of patients with monophasic NMO as well as MS patients showing optic-spinal involvement over the 30-year period. The decreases in the proportion of patients with monophasic NMO and the absolute number of monophasic NMO patients over the four-survey period are considered to indicate a real decrease in the prevalence of this condition, possibly resulting from environmental changes during the rapid "Westernization" of Japan. Since the classification criteria for relapsing OSMS were first proposed in 1996[4], this phenotype was not classified separately in the previous three surveys, meaning that the frequencies of the relapsing OSMS phenotype could not be compared among the four surveys. However, the fourth nationwide survey revealed that the absolute numbers of

OSMS patients were unchanged over a wide range of birth years among southern patients, while only a modest decrease was observed with advancing year of birth among northern patients. These findings suggest that the changes in environmental factors responsible for the drastic decrease in the prevalence of monophasic NMO may not have equally lessened the occurrence of relapsing OSMS among Japanese.

CONCLUSION

In conclusion, the temporal changes and geographical differences in MS phenotypes suggest that susceptibility to the CMS phenotype and brain lesion burdens can be altered drastically over a relatively short period and in particular areas by environmental factors. "Westernization", which is likely to have reinforced the Western MS phenotype, has taken place equally in northern and southern parts of Japan. Nonetheless, the emergence of Western-type MS appears to be happening faster in the north, suggesting that latitude or latitude-related factors could be influential in determining MS phenotypes, even in races resistant to MS. Interestingly, the MRI features characteristic of Western-type and Asian-type MS, namely Barkhof brain lesions and LESCLs, respectively, appeared to be differentially influenced by changes in environmental factors because the former, which are markedly enhanced in northern-born northern-residents, are also augmented by a "Westernized" environment, in which today's young generation are being raised, while development of the latter is less affected or unaffected by such changes.

ACKNOWLEDGMENTS

REFERENCES

1. Kira J. Multiple sclerosis in the Japanese population. *Lancet Neurol* 2003; 2:117-27.
2. Okinaka S, Tsubaki T, Kuroiwa Y, Toyokura Y, Imamura Y, Yoshikawa M. Multiple sclerosis and allied diseases in Japan. Clinical characteristics. *Neurology* 1958; 8:756-63.
3. Shibasaki H, Kuroiwa Y. Clinical studies of multiple sclerosis in Japan. II. Are its clinical characteristics changing? *Neurology* 1973; 23:618-22.
4. Kira J, Kanai T, Nishimura Y, Yamasaki K, Matsushita S, Kawano Y *et al*. Western versus Asian types of multiple sclerosis: immunogenetically and clinically distinct disorders. *Ann Neurol* 1996; 40:569-74.
5. Lennon VA, Wingerchuk DM, Kryzer TJ, *et al*. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004; 364:2106-12.
6. Nakashima I, Fujihara K, Miyazawa I, *et al*. Clinical and MRI features of Japanese patients with multiple sclerosis positive for NMO-IgG. *J Neurol Neurosurg Psychiatry* 2006; 77:1073-5.
7. Matsuoka T, Matsushita T, Kawano Y, *et al*. Heterogeneity of aquaporin-4 autoimmunity and spinal cord lesions in multiple sclerosis in Japanese. *Brain* 2007; 130:1206-23.
8. Weinshenker BG, Wingerchuk DM, Nakashima I, Fujihara K, Lennon VA. OSMS is NMO, but not MS: proven clinically and pathologically. *Lancet Neurol* 2006; 5: 110-1.
9. Kikuchi S, Fukazawa T. "OSMS is NMO, but not MS": confirmed by NMO-IgG? *Lancet Neurol* 2005; 4: 594-5.
10. Compston A. Complexity and heterogeneity of demyelinating disease. *Brain* 2007; 130:1178-80.
11. Kuroiwa Y, Igata A, Itahara K, Koshijima S, Tsubaki T. Nationwide survey of multiple sclerosis in Japan. Clinical analysis of 1,084 cases. *Neurology* 1975; 25:845-51.
12. Shibasaki H, Kubo N, Nishitani H, Saida T, Ohno Y, Fukuyama Y. Nationwide survey of multiple sclerosis in Japan: reappraisal of clinical features. *J Trop Geo Neurol* 1992; 2:73-82.
13. Schumacher GA, Beebe GW, Kibler RF, *et al*. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann N Y Acad Sci* 1965; 122:552-68.
14. Osoegawa M, Kira J, Fukazawa T, *et al*. Temporal changes and geographical differences in multiple sclerosis phenotypes in Japanese: nationwide survey results over 30 years. *Mult Scler* (In press).
15. McDonald WI, Compston A, Edan G, *et al*. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; 50:121-7.
16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33:1444-52.
17. Barkhof F, Filippi M, Miller DH, *et al*. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 1997; 120:2059-69.