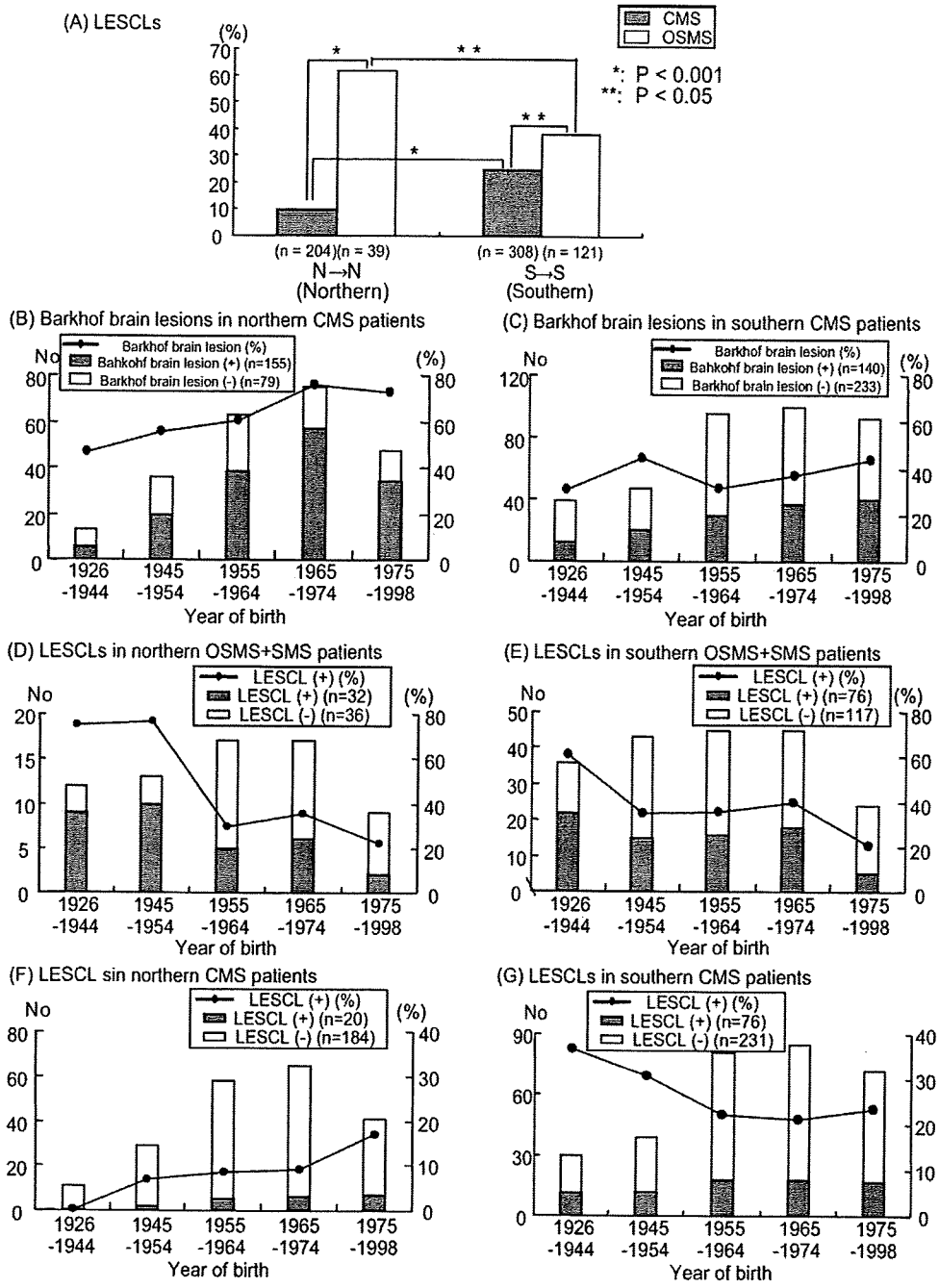

Supplementary Figure 1 Frequencies of longitudinally extensive spinal cord lesions (LESCLs) on MRI (A) in northern-born northern residents (N• N) (northern patients), southern-born southern residents (S• S) (southern patients), northern-born southern residents (N• S), and southern-born northern residents (S• N). The difference in the frequencies of LESCLs between patients with OSMS and patients with CMS is marked in northern patients, but rather small in southern patients. Changes in the proportions and absolute numbers of CMS patients with Barkhof brain lesions in relation to birth year among northern (B) and southern (C) patients. Changes in the proportions and absolute numbers of OSMS+SMS patients with LESCLs in relation to birth year among northern (D) and southern (E) patients. Proportions and absolute numbers of CMS patients with LESCLs among northern (F) and southern (G) patients. In (B)–(G), bars indicate the absolute number in each group with the indicated birth years, while dotted lines show the changes in the positive percentages of the indicated groups. CMS, conventional multiple sclerosis; LESCLs, longitudinally extensive spinal cord lesions extending for three or more vertebral segments on MRI; n, number of patients whose information was obtained; OSMS, optic-spinal multiple sclerosis; SMS, spinal multiple sclerosis.

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

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

female to male ratio increases rapidly with advancing year of birth in Canada, implicating the importance of environmental factors in early life for causing a disproportionate increase in the number of female patients with MS. An "anticipation" of age at onset was also observed in Sardinia [40], where rapid increases in the incidence and prevalence of MS over recent decades were noted [41]. Intriguingly, when individuals with ancestors originating from regions where MS is rare are raised in a region of high MS prevalence, the age at onset of MS is reported to decrease [42]. Therefore, it is possible that susceptibility to MS has increased among younger Japanese females raised in a modern Westernized environment, resulting in earlier ages at onset.

Subtype classification of MS based on symptomatology inevitably results in some ambiguity in the classification of individual cases by different institutions, and such arbitrariness in the classification may produce equivocal results. To minimize this limitation, clinical classifications were performed in all cases by the central office reviewing the collated information. Concerning the grouping of clinical symptomatology-based subtypes, patients with SMS had similarities to patients with OSMS in terms of demographic features, including MRI characteristics, whereas patients with BSMS and patients with OBSMS showed similarities to patients with CMS. In addition, comparison of patients with OSMS+SMS and patients with CMS+BSMS+OBSMS gave practically the same results as the comparison of patients with OSMS and CMS in terms of their distributions by latitude and year of birth. Therefore, we consider that although ambiguity and limitation inherent to such clinical classification and grouping should be cautiously judged, the methodology used in the present study is generally adequate for dealing with the large number of patients with MS collated from all over the country. The four nationwide surveys in Japanese included NMO according to the identical diagnostic criteria within the MS spectrum. However, the nosological positions of NMO and OSMS are less certain [9,10]. The present survey could not incorporate testing for either NMO-IgG or antibodies against the relevant autoantigen, aquaporin-4 (AQP4), because it had not been discovered when this survey was initiated. However, recent studies from Japan have shown that approximately 50% of patients with OSMS with LESCLs are negative for anti-AQP4 antibodies [8,43] and NMO-IgG or anti-AQP4 antibody-positive patients with MS frequently have periventricular ovoid lesions in the brain and short spinal cord lesions in addition to LESCLs, suggesting that there is still some overlap between NMO-IgG-positive and -negative patients with MS, at least among Japanese [8]. Therefore, although future epidemiological surveys of demyelinating diseases need to include an anti-AQP-4 antibody assay, successive nationwide surveys encompassing the NMO phenotype within the MS spectrum, based on their identical inclusion criteria, still seem to be relevant.

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

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

One of the most important findings in the present study is the large increase in the number of patients with classical type MS harboring Barkhof brain lesions because this increase showed distinctive patterns according to geography and year of birth. The differential increase in the prevalence of the CMS phenotype based on year of birth is consistent with the results of two small regional-scale studies performed in Japan that revealed increased numbers of cases of CMS relative to the numbers of OSMS cases [44,45] and cannot be explained by ascertainment bias alone. The present nationwide survey showed, for the first time, that the amount

of this 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 indicate the presence of environmental factors predisposing people in the north to Western-type MS. The results of the multiple logistic analyses strongly support the presence of factors predisposing people in the north to the development of MS-like brain lesions. Although the timing of migration was not specified in the present survey, 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, a fact that first became apparent in those born after World War II in the north, and only recently became apparent in the south. These findings point to a corresponding change in the distribution of environmental factors in Japan, especially in the north.

Another important issue is the trend toward decreased proportions of patients with monophasic NMO as well as patients with MS showing optic-spinal involvement across the four nationwide surveys over the 30-year period. Regarding patients with monophasic NMO, not only patients with onset during the survey year but also those who were previously diagnosed and visited hospitals for a regular follow-up during the survey year were enrolled. Therefore, the period of observation of these patients in the present survey was 9.5 ± 9.2 years, which is assumed to be long enough to distinguish between monophasic NMO and relapsing OSMS in most patients. Thus, the decreases in the proportions of patients with monophasic NMO and the absolute number of monophasic NMO patients over the four survey periods 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 [5], 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 showed that the absolute numbers of patients with OSMS were actually unchanged over the wide range of birth years among southern patients, whereas only a modest decrease was observed with advancing year of birth among northern patients. These findings suggest the possibility 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. Although the relationships among monophasic and relapsing NMO and OSMS are still obscure, it has been reported that patients with monophasic NMO and those with relapsing NMO have significantly different autoimmune backgrounds [46]. Thus, it seems feasible that patients with monophasic NMO and those with relapsing OSMS have distinct susceptibilities to changes in environmental factors.

The present survey confirmed the frequent occurrence of LESCLs in Japanese patients with MS. Specifically, these lesions were much more common in patients with OSMS, but were also clearly evident even among patients with CMS. LESCLs are exceptional in MS in Western patients [47] but are more common in Asian patients [8,48,49]. Indeed, in the present study, multiple logistic analyses showed that factors characteristic of Asian type MS, such as marked CSF pleocytosis, OSMS phenotype, and higher EDSS score [2], were strongly related to the development of LESCLs, whereas heightened CSF IgG response, a consistent finding in patients with Western type MS [1], was negatively associated. These findings indicate that LESCLs are one of the decisive denominators of Asian type MS. In the present study, the presence of LESCLs was assessed during the entire course, which possibly resulted in an underestimation of their frequency because not all spinal cord MRI scans were taken during the acute phase. However, we consider that the approximately three-fold difference in LESCL frequency between patients with OSMS and patients with CMS would not be largely distorted by this underestimation.

Regarding the differences in the MS phenotypes associated with year of birth, although the absolute numbers of patients with OSMS and those with LESCLs as a whole were largely unchanged over the wide range of birth years, the absolute numbers of patients with OSMS+SMS with LESCLs showed a tendency to decrease with advancing year of birth, whereas the numbers of patients with CMS with LESCLs increased with advancing year of birth among northern patients; these trends were minimal among southern patients. Anti-AQP4 antibody-positive NMO patients can exhibit extra-optic-spinal manifestations, which may account for the presence of patients with CMS with LESCLs. However, because anti-AQP4 antibody-positive patients usually show a higher age at onset [8], the increased prevalence of CMS with LESCLs among

the younger generation cannot be explained solely by the inclusion of such antibody-positive patients. Even in the Western literature, there is a recent report describing the presence of diffuse spinal cord lesions in 13% of Caucasian patients with MS in whom the OSMS presentation is rare [50]. Considering the large increase in the total number of patients with MS, it is conceivable that phenotypic changes in clinically definite patients with MS are, for the most part, attributable to the increased occurrence of CMS in the younger generation, which is in keeping with the increased prevalence of Barkhof brain lesions in these populations. However, although small changes in the absolute number should be interpreted cautiously, the emergence of patients with intermediate phenotypes, such as CMS with LESCLs and OSMS+SMS without LESCLs, in place of decreasing numbers of patients with prototypic Asian type MS (OSMS with LESCLs) is assumed to have occurred in the north. The higher frequencies of OBSMS and BSMS and other possible intermediate forms, among northern patients compared with southern patients, may also have occurred in place of decreasing numbers of patients with prototypic Asian type MS. Collectively, these observations suggest the possibility that a shift from the OSMS phenotype to the CMS phenotype through intermediate phenotypes is also occurring among northern patients. The presence of intermediate phenotypes could be partly related to the limitations of the clinical classification on the one hand, while on the other hand, it may indicate an overlap between CMS and OSMS thereby suggesting that CMS and OSMS are within a spectrum of the disease.

Changes in the distributions of factors predisposing people to Western type MS appear to have occurred preferentially in the north. The aboriginal people, known as the Ainu, of the northernmost island (Hokkaido) of the Japanese archipelago are a minor ethnic population distinct from mainland Japanese. They make up approximately 0.01% of the northern Japanese population at present [51]. Although earlier anthropological observations based on morphological features determined that the Ainu were Caucasian descendents, recent genetic studies have shown close relationships to both North Asians and mainland Japanese [52,53]. Moreover, most residents of Hokkaido are descendants of migrants from all over mainland Japan who went to the Hokkaido area during and after the Meiji era (1868–1912), about a century ago. Therefore, the influence of the genetic admixture on phenotypic changes in northern patients appears to be modest, but cannot be completely excluded. Since patients born before the end of World War II have similar clinical features in the north and south, environmental changes that predispose people to MS have preferentially occurred thereafter in the north, or alternatively, northern people are intrinsically more susceptible to such exogenous changes than southern people.

In summary, 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 environmental factor changes, since the former, which are markedly enhanced in northern-born northern residents, is also augmented by a "Westernized" environment, in which the younger generation are being raised, whereas development of the latter is less affected or unaffected by such changes. Future nationwide surveys incorporating anti-AQP4 antibody assays and detailed MRI analyses in Japanese will provide further insights into the mechanisms underlying the phenotypic changes in MS induced by the environment.

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Appendix

The chairmen of the previous nationwide survey committees were Professors Yoshigoro Kuroiwa (Department of Neurology, Kyushu University; first survey), Akihiro Igata (Third Department of Internal Medicine, Kagoshima University; second survey), and Hiroshi Nishitani (Department of Neurology, National Utano Hospital; third survey). In the fourth survey, in addition to the authors, the following were members of the Research Committee of Neuroimmunological Diseases: Drs Susumu Chiba (Department of Neurology, School of Medicine, Sapporo Medical University), Dr Yoshitaka Fujii (Department of Surgery II, Nagoya City University Medical School), Susumu Furukawa (Department of Pediatrics, Yamaguchi University School of Medicine), Hideo Hara (Department of Vascular Dementia Research, National Institute for Longevity Sciences, National Center of Geriatrics and Gerontology), Toshirou Hara (Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University), Kinya Hisanaga (Department of Neurology, Miyagi National Hospital), Shu-ichi Ikeda (Department of Neurology, Shinshu University School of Medicine), Shuji Izumo (Division of Molecular Pathology, Center for Chronic Viral Diseases, Graduate School of Medical and Dental Sciences, Kagoshima University), Ryuji Kaji (Department of Neurology, Graduate School of Medicine, Tokushima University), Takashi Kanda (Department of Neurology and Clinical Neuroscience, Yamaguchi University School of Medicine), Shosei Koh (Department of Biomedical Laboratory Sciences, School of Medicine, Shinshu University), Susumu Kusunoki (Department of Neurology, Kinki University School of Medicine), Satoshi Kuwabara (Department of Neurology, Chiba University School of Medicine), Hidenori Matsuo (Division of Clinical Research, Nagasaki Medical Center of Neurology), Hidehiro Mizusawa (Department of Neurology and Neurological Science, Graduate School, Tokyo Medical and Dental University), Tatsufumi Nakamura (Department of Molecular Microbiology and Immunology, Graduate School of Biomedical Sciences, Nagasaki University), Kyoichi Nomura (Department of Neurology, Saitama Medical School), Mieko Ogino (Department of Internal Medicine III (Neurology), Kitasato University School of Medicine), Yoshiro Ohara (Department of Microbiology, Kanazawa Medical University), Mitsuhiro Osame (Department of Neurology and Geriatrics, Kagoshima University School of Medicine), Kohei Ota (Department of Health Science, Faculty of Science, Tokyo University of Science), Jun Shimizu (Department of Neurology, University of Tokyo), Akio Suzumura (Department of Neuroimmunology, Research Institute of Environmental Medicine, Nagoya University), Takeshi Tabira (Department of Vascular Dementia Research, National Institute for Longevity Sciences, National Center of Geriatrics and Gerontology), Keiko Tanaka (Department of Neurology, Brain Research Institute, Niigata University), Masami Tanaka (Department of Neurology and Clinical Research Center, Nishi-Niigata Chuo National Hospital), Makoto Yoneda (Second Department of Internal Medicine, Faculty of Medical Sciences, University of Fukui), Hiroaki Yoshikawa (Health Service Center, Kanazawa University), and Nobuhiro Yuki (Department of Neurology and Research Institute for Neuroimmunological Diseases, Dokkyo Medical University School of Medicine).

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Heterogeneity and continuum of multiple sclerosis phenotypes in Japanese according to the results of the fourth nationwide survey

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abstract

There are two distinct phenotypes of multiple sclerosis (MS) in Asians, optic-spinal MS (OSMS) and conventional MS (CMS). In 2004, we performed the fourth nationwide epidemiological survey of MS. The epidemiological features were reported elsewhere; here we report the characteristic features of patients with each MS phenotype, classified according to the clinically estimated sites of involvement and MRI findings. Among 1493 MS patients collated, 57.7% were classified as having CMS and 16.5% were classified as having OSMS. Based on MRI findings, MS patients were further subdivided into those with OSMS with or without longitudinally extensive spinal cord lesions (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 LESCLs, 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, 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 demographic features not only vary based on CMS or OSMS phenotype, but also with the presence or absence of LESCLs, and that nonetheless, these four phenotypes constitute a continuum.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). MS is rare in Asians, but when it appears, involvement of the optic nerve and spinal cord is destructive [1]. There are two distinct subtypes of MS in Asians: the optic-spinal form (OSMS), which shows selective involvement of the optic nerve and spinal cord, and the conventional form (CMS), which affects multiple sites of the central nervous system (CNS), including the cerebrum and cerebellum [2]. The two subtypes have distinct clinical and neuroimaging features. OSMS is characterized by a higher age at onset, greater female preponderance and higher Kurtzke's Expanded Disability Status Scale (EDSS) score [3] compared with CMS [1,2]. Longitudinally extensive spinal cord lesions (LESCLs) extending over three or more vertebral segments are more commonly found in patients with OSMS than CMS patients [1]. However, reflecting the pronounced spinal cord damage seen in Asians, one-fourth of CMS patients also have such LESCLs [4,5].

In Japan, nationwide surveys of MS were conducted in 1972, 1982, 1989 and 2004 using essentially identical criteria [6-8]. In the fourth survey, we disclosed a four-fold increase in the estimated number of clinically definite MS patients (9900; crude MS prevalence, 7.7/100,000) in 2003 compared with 1972, and a shift in the peak age at onset from early 30 s in 1989 to early 20 s in 2003 [8], suggesting an

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Table 1
Clinical characteristics among each multiple sclerosis 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%)*b	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%)*a, *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 • uid • ndings				
Marked pleocytosis (• 50 WBC/mm^3) or neutrophilia (• 5 neutrophils/mm^3)	16/79 (20.3%)*a, *e	3/96 (3.1%)*a, *l	17/102 (16.7%)*b, *l	21/511 (4.1%)*b, *e
Increased IgG index	12/45 (26.7%)*e	16/51 (31.4%)*d	29/59 (49.2%)	186/298 (62.4%)*d, *e
Brain MRI • ndings				
• 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, *f	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 ful• lling 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 • ndings				
• 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 = expanded disability status scale of Kurtzke; Gd = gadolinium; LESCLs = longitudinally extensive spinal cord lesions extending 3 or more vertebral segments; N.S. = not signi• cant; OSMS = optic-spinal form of multiple sclerosis.
*a: Pb0.01 (OSMS with LESCLs vs. OSMS without LESCLs), *b: Pb0.01 (CMS with LESCLs vs. CMS without LESCLs), *c: Pb0.01 (OSMS with LESCLs vs. CMS with LESCLs), *d: Pb0.01 (OSMS without LESCLs vs. CMS without LESCLs), *e: Pb0.01 (OSMS with LESCLs vs. CMS without LESCLs), *f: Pb0.01 (OSMS without LESCLs vs. CMS with LESCLs), *g: 0.01 • Pb0.05 (OSMS with LESCLs vs. OSMS without LESCLs), *h: 0.01 • Pb0.05 (CMS with LESCLs vs. CMS without LESCLs), *i: 0.01 • Pb0.05 (OSMS with LESCLs vs. CMS with LESCLs), *j: 0.01 • Pb0.05 (OSMS without LESCLs vs. CMS without LESCLs), *k: 0.01 • Pb0.05 (OSMS with LESCLs vs. CMS without LESCLs), *l: 0.01 • Pb0.05 (OSMS without LESCLs vs. CMS with LESCLs).

increase in susceptibility to this disease among the younger generation. In this study, a successive decrease in optic-spinal involvement in clinically de• nite MS patients was also revealed, while the absolute numbers of CMS patients and those with MS-like brain lesions ful• lling the Barkhof criteria were found to increase rapidly with advancing year of birth. Also, the frequency of LESCLs was found to be signi• cantly higher in OSMS patients than in CMS patients in this nationwide survey.

We recently reported that there are distinct subtypes of MS according to clinical and MRI • ndings using our institutional series of MS patients [9,10]. Therefore, in the present study, we aimed to clarify the characteristic features of each MS phenotype classi• ed according to the clinically estimated sites of involvement and MRI • ndings unique to Asian MS patients, such as the presence or absence of LESCLs, using collated MS cases from the fourth nationwide survey of MS in Japan.

2. Methods

2.1. Survey procedures

The fourth nationwide survey of MS was conducted by the Research Committees of Neuroimmunological Diseases and of Epidemiology of Intractable Diseases, sponsored by the Ministry of Health, Labor and Welfare, Japan. The study was approved by the Kyushu University Ethics Committee. The survey was undertaken in two steps: • rst, a preliminary survey was undertaken to ascertain the approximate number of MS patients in Japan, and second, a survey was conducted using a questionnaire sheet for each patient. The hospitals included in the study were randomly selected from the directory of all of the registered hospitals throughout Japan. Selection was made according to a strati• cation based on the number of beds in each hospital; the more beds a hospital had, the higher was its probability of being selected [11]. Sampling rates were approximately 8%, 13%, 24%, 43%, 83% and 100% for the strata of general hospitals with 20 to 99 beds, 100 to 199 beds, 200 to 299 beds, 300 to 399 beds, 400 to 499 beds and 500+ beds, respectively. All university hospitals, including those in which council members of the Japanese Society of Neurology and members of the Committees of Medical Facilities for Children and the Japanese Society of Child Neurology were working, were also surveyed.

The questionnaire for the preliminary survey on MS patients who visited hospitals because of the disease in 1 year from 1 January to 31 December 2003 was mailed to 6708 departments (including 1933 neurology/internal medicine, 1227 orthopedics, 997 psychiatry, 945 pediatrics, 831 ophthalmology, 759 neurosurgery and 16 rehabilitation departments), together with the diagnostic criteria, in January 2004. In Japan, all patients with MS are requested to visit hospitals at

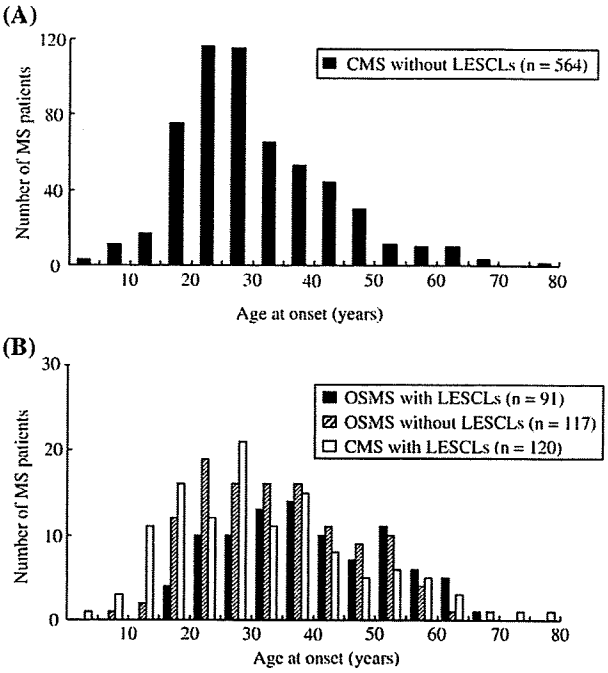

Fig. 1. Distribution of age at onset in patients with CMS without LESCLs (A), CMS without LESCLs, OSMS patients with LESCLs and OSMS patients without LESCLs (B). In (A) and (B), "anticipation" of age at onset is more pronounced in patients without LESCLs, irrespective of CMS or OSMS phenotype. The second peak around the early 50 s is not evident in CMS patients without LESCLs, but is still identi• able in the other three subtypes. CMS = conventional form of multiple sclerosis, LESCLs = longitudinally extensive spinal cord lesions extending three or more vertebral segments on MRI, n = number of patients on whom information was obtained, and OSMS = optic-spinal form of multiple sclerosis.

least once every year for registration of intractable diseases with the government in order to have their medical costs, which are not covered by health insurance, subsidized. Following the collection and collation of the • rst questionnaire, the second questionnaire was forwarded to those institutions reporting patients in the • rst survey. It requested detailed clinical information on individual patients, including age at onset and examination, sex, birthplace, present address, symptoms based on history and signs based on physical examination, laboratory • ndings, course, treatment and prognosis. Patients reported by more than one hospital or department were treated as duplicates.

2.2. Diagnostic criteria

The diagnostic criteria used for the present survey were based on those used for the • rst nationwide survey in 1972 [6], except that the limitation of age at onset was removed, as it was in the third survey [7]. The criteria required multiplicity in time and space and were essentially the same as Schumacher's criteria [12]. Brie• y, the criteria used for relapsing remitting multiple sclerosis (MS) in the present survey consisted of three items for clinically de• nite MS: (1) symptoms and signs owing to multifocal lesions in the CNS (more than two lesions in the CNS); (2) remissions and exacerbations (multiplicity in time); and (3) other diseases, such as tumors, syphilis, cerebrovascular accident, cervical spondylosis, angiomas, subacute myelo-optico-neuropathy, neuro-Behçet, cerebellar degeneration, HTLV-I-associated myelopathy/tropical spastic paraparesis and collagen diseases, could be excluded. Clinically de• nite MS ful• lled all of the criteria, while a diagnosis of possible MS was made when all three criteria for clinically de• nite MS could not be ful• lled, but the signs were suggestive. The criteria concerning primary progressive MS (PPMS) were the same as McDonald's criteria [13].

2.3. Classi• cation of clinical phenotype

Clinical classi• cation of MS subtypes was based solely on the clinically estimated sites of the lesions. The second questionnaire asked answerers to report the clinically estimated sites of the lesions according to the symptomatology during the entire clinical course from among the following: optic nerve, cerebrum, cerebellum, brainstem and spinal cord. Moreover, the questionnaire also asked answerers to check for the presence of any of the signs and symptoms listed in the footnote to Table 1, during the entire clinical course. The survey center classi• ed 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. If there was no information about lesion sites, or the symptoms and signs during the entire course were incompatible with the lesion sites, the cases were placed into the unclassi• ed category.

In the preliminary survey, 3749 institutions (55.9%) responded, and reported 4827 MS patients, including 849 patients with possible MS. In the second questionnaire, detailed data were collated for 1919 patients (39.3% of those in the preliminary survey), including 30 duplicate cases. The estimated number of clinically de• nite MS patients in 2003 was 9900 (95% CI: 9100–10,700) and the estimated crude prevalence was 7.7/100,000 (95% CI: 7.1–8.4) [8]. Based on the clinically estimated sites of lesions, 1493 patients with clinically de• nite MS and completed questionnaires were classi• ed as having CMS (57.7%), OBSMS (5.8%), BSMS (4.6%), OSMS (16.5%), SMS (10.6%) or unclassi• ed MS (4.9%). In the present study, both CMS and OSMS patients were subjected to further analyses.

2.4. MRI • nding-based classi• cation

We recently published a purely MRI • ndings-based classi• cation in our institutional MS series to minimize the ambiguity of clinical • nding-based classi• cation [10]; therefore, we applied such an MRI • nding-based classi• cation to the present Japanese nationwide survey series. In the present study, MS patients were classi• ed according to the presence or absence of LESCLs as well as the presence or absence of brain lesions ful• lling the Barkhof criteria (brain lesions ful• lling the Barkhof criteria = Barkhof brain lesions (+)). MS patients were classi• ed into four groups based on MRI • ndings, Barkhof(+)LESCL(+), Barkhof (+) LESCL(•), Barkhof(•)LESCL(+), and Barkhof(•)LESCL(•), and we compared the demographic features among these groups. To conduct MRI • nding-based classi• cation and analyses, longitudinally extensive spinal cord lesions (LESCLs) were de• ned as those extending over three or more vertebral segments on MRIs taken during the entire clinical course. Ful• llment of the Barkhof criteria [14] was assessed by the central of• ce according to the MRI • ndings described in the answer sheets. In this analysis, not only patients with OSMS and CMS, but also those with OBSMS, BSMS and SMS, were included.

2.5. Statistical analysis

Statistical analyses of numerical variables were initially performed using the Kruskal–Wallis H test. When statistical signi• cance was found, the Mann–Whitney U test was used to determine the statistical signi• cance of differences between subgroups. Uncorrelated P values were corrected by multiplying them by the number of comparisons

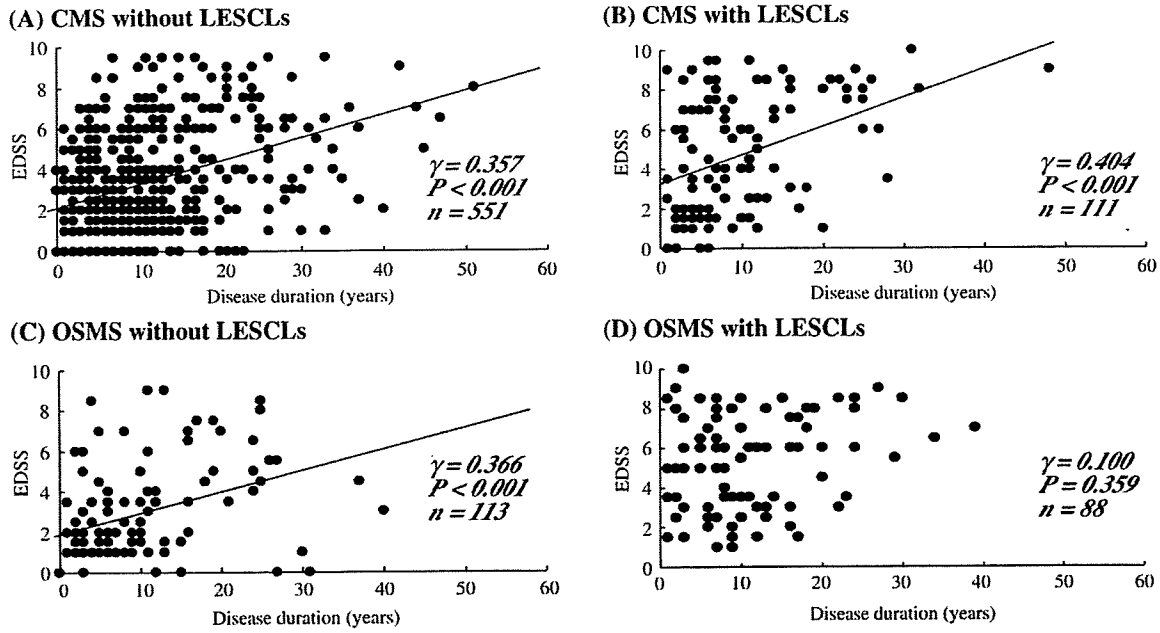

Fig. 2. Relationship between EDSS scores and disease duration in patients with each MS subtype. (A) CMS without LESCLs. (B) CMS with LESCLs. (C) OSMS without LESCLs. (D) OSMS with LESCLs. All patients except OSMS patients with LESCLs show a highly signi• cant correlation between the two parameters. CMS = conventional form of multiple sclerosis, EDSS = Expanded Disability Status Scale of Kurtzke, LESCLs = longitudinally extensive spinal cord lesions extending three or more vertebral segments on MRI, n = number of patients on whom information was obtained, and OSMS = optic-spinal form of multiple sclerosis.

(Bonferroni–Dunn's correction) to calculate corrected P values. Differences in the ratios between two groups were tested for signi• cance by the • ^{2} test or the Fisher's exact test when the criteria for the • ^{2} tests were not ful• lled.

3. Results

3.1. Demographic features of each MS subtype

Based on the MRI • ndings, MS patients were subdivided into those with OSMS with or without LESCLs and those with CMS with or without LESCLs (Table 1). The proportion of females was signi• cantly greater among OSMS or CMS patients with LESCLs than among CMS patients without LESCLs (P^{corr}b0.05 in OSMS with LESCLs and P^{corr}b0.05 in CMS with LESCLs). Age at onset was signi• cantly higher in OSMS patients with LESCLs than in other patient groups (P^{corr}b0.05). The peak age at onset was early 20 s among CMS or OSMS patients without LESCLs, late 20 s among CMS patients with LESCLs, and late 30 s among OSMS patients with LESCLs (Fig. 1A, B). A second peak in the early 50 s was identi• able in all groups except for CMS patients without LESCLs.

Although disease duration did not differ signi• cantly among the four groups, EDSS scores were signi• cantly higher in patients with LESCLs than in those without LESCLs, irrespective of OSMS or CMS phenotype (P^{corr}b0.01). Occurrences of bilateral visual loss, transverse myelitis, paraparesis, sensory level and sphincter disturbance were highest in OSMS patients with LESCLs among the four groups (P^{corr}b0.01 in all comparisons). CMS patients with LESCLs also showed signi• cantly higher frequencies of these symptoms than CMS patients without LESCLs (P^{corr}b0.01 in all). Bilateral visual loss and transverse myelitis were signi• cantly more common in OSMS patients without LESCLs than in CMS patients without LESCLs (P^{corr}b0.01 in both). Secondary progression was more common in CMS patients than OSMS patients, regardless of the presence or absence of LESCLs (P^{corr}b0.05, OSMS without LESCL vs. CMS with or without LESCL). There was a signi• cant positive correlation between EDSS scores and disease duration in all groups (Pb0.0001), with the exception of OSMS patients with LESCLs (Fig. 2).

3.2. Laboratory • ndings in each MS subtype

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}b0.05 in all). Increased IgG index and brain lesions ful• lling the Barkhof criteria [14] 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}b0.01 in all). Even when MS patients with a disease duration of less than 10 years were excluded, more OSMS patients showed a lack of brain lesions than CMS patients (53.8% of OSMS patients with LESCLs, 34% of OSMS patients without LESCLs, 2.1% of CMS patients with LESCLs, and 2.1% of CMS patients without LESCLs, P^{corr}b0.01 in all comparisons), while there were fewer OSMS patients than CMS patients with Barkhof brain lesions (5.1% of OSMS patients with LESCLs, 6.4% of OSMS patients without LESCLs, 51.1% of CMS patients with LESCLs, and 54.4% of CMS patients without LESCLs, P^{corr}b0.01 in all comparisons), regardless of the presence or absence of LESCLs. Gadolinium enhancement of the spinal cord lesions was signi• cantly more common in patients with LESCLs than in those without, irrespective of clinical phenotype (P^{corr}b0.01 in all).

3.3. Comparison of demographic features among MS patients with contrast-enhanced spinal cord lesions

To focus on in• ammatory spinal cord lesions, we compared the demographic features of MS patients with contrast-enhanced spinal cord lesions according to the clinical classi• cation of OSMS or CMS and MRI • ndings of LESCL positivity. We found essentially the same tendency in this analysis as in the analysis of all the spinal cord lesions, but lost some statistical signi• cance owing to the small sample size (Supplementary Table).

3.4. Comparison of the demographic features of MS patients according to MRI • nding-based classi• cation

We • nally classi• ed MS patients according to two hallmark MRI • ndings: brain lesions ful• lling the Barkhof criteria and LESCLs (Table 2). The former is the characteristic feature of Western MS, while the latter is characteristic of Asian MS.

The proportion of females was highest in the Barkhof(+)LESCL(+) group, but no signi• cant difference was found among the four groups. The age at onset was higher in the Barkhof(•)LESCL(+) group than in any other group (P^{corr} b0.01 in all comparisons). Although the disease duration was not signi• cantly different among the four groups, the EDSS scores were signi• cantly higher in patients with LESCLs than in those without LESCLs, irrespective of the presence or absence of Barkhof brain lesions (P^{corr} b0.01 in all comparisons). Likewise, the frequencies of bilateral visual loss, transverse myelitis, paraparesis, quadriparesis, sensory level and sphincter disturbance were signi• cantly higher in patients with LESCLs than in those without LESCLs, regardless of the presence or absence of Barkhof brain lesions (P^{corr} b0.05 in all comparisons). By contrast, the frequency of secondary progression was signi• cantly higher in patients with Barkhof brain lesions than those without Barkhof brain lesions (P^{corr} b0.05 in all comparisons). Marked CSF pleocytosis and CSF neutrophilia were more frequent in the Barkhof(•)LESCL(+) group than the Barkhof (+)LESCL(•) and Barkhof(•)LESCL(•) groups (P^{corr} b0.01 in all comparisons), while the frequency of increased IgG index was signi• cantly more common in the Barkhof (+)LESCL(•) group than the Barkhof(•)LESCL(+) and Barkhof(•)LESCL(•) groups (P^{corr} b0.01 in all comparisons).

4. Discussion

In the present study, using MS cases collated in the fourth nationwide survey in Japan, we disclose that distinct demographic features vary not only with clinical phenotype, such as OSMS and CMS, but also with the characteristic MRI • ndings, such as LESCLs and Barkhof brain lesions.

The present study had some limitations, primarily because the response rate in the second survey was not high. Concerning the relatively low response rate to this type of nationwide epidemiological survey in Japan, the assumption that the mean number of patients among responding hospitals is equal to that among non-responding hospitals has already been validated [15]. Therefore, we consider that our results would not be distorted seriously by the relatively low response rates. Second, the study was inevitably limited by the fact that the questionnaires were answered by many different clinicians across the country: 88% of the questionnaires were collected from neurologists, 70% of whom had previously participated in a randomized controlled trial of interferon beta-1b [16], which increases the quality of the data, but unfortunately produces a selection bias.

Subtype classi• cation of MS based on symptomatology tends to have some ambiguity and arbitrariness, which may produce equivocal results. To minimize such a limitation, clinical classi• cation was performed in all cases by the central of• ce reviewing collected information. The present survey could not incorporate testing for either neuromyelitis optica (NMO)-IgG or anti aquaporin-4 (AQP4) antibody [17,18], which had not yet been discovered when this survey was initiated. As NMO-IgG, a newly identi• ed marker for NMO [17,18], was also detected in a fraction of Japanese OSMS patients [19], OSMS is claimed to be the same disease as relapsing NMO [20]. However, recent studies from Japan have revealed that about half of OSMS patients with LESCLs are negative for anti-AQP4 antibodies [21,22], and that both NMO-IgG- and anti-AQP4 antibody-positive MS patients frequently have periventricular ovoid lesions in the brain and short spinal cord lesions in addition to LESCLs, suggesting that there is still some overlap between NMO-IgG-positive and -negative MS patients, at least among Japanese [21]. Given that these limitations exist, a nationwide survey collating a large number of Asian MS cases, including MRI • ndings for the • rst time, seems to still be relevant, especially cases of CMS, who rarely have NMO-IgG/anti-AQP4 antibody [21].

Table 2
Clinical features among each multiple sclerosis subgroups classi• ed according to the characteristic MRI • ndings.

	Barkhof MRI lesion (+)		Barkhof MRI lesion (•)	
	LESCL (+) (n = 64)	LESCL (•) (n = 342)	LESCL (+) (n = 213)	LESCL (•) (n = 491)
Sex ratio (male:female)	1:4.8	1:2.3	1:3.7	1:3.1
Age at onset (years)	29.5 ± 15.4*c	28.5 ± 11.4*d,*f	37.8 ± 13.8*b,*c, *f	32.0 ± 12.3*b,*d
Age at examination (years)	40.7 ± 15.6*c	39.1 ± 12.4*f	47.3 ± 14.2*b,*c, *f	41.2 ± 12.8*b
Disease duration (years)	11.2 ± 7.7	10.6 ± 8.2*j	9.7 ± 8.2	9.2 ± 7.7*j
EDSS scores	4.7 ± 3.0*a,*e	3.4 ± 2.5*a,*d,*f	4.9 ± 2.6*b,*f	2.7 ± 2.3*b,*d,*e
Symptoms during entire course				
Bilateral visual loss	29/64(45.3%)*a, *k	86/340 (25.3%)*a,*f	87/213 (40.8%)*b,*f	131/481 (27.2%)*b,*k
Transverse myelitis	30/63 (47.6%)*a, *e	47/335 (14.0%)*a, *d,*f	115/207 (55.6%)*b,*f	115/478 (24.1%)*b,*e, *c
Paraparesis	36/61 (59.0%)*e	146/335 (43.6%)*f	133/207 (64.3%)*b,*f	166/481 (34.5%)*b,*d,*c
Quadriparesis	23/62 (37.1%)*a, *e	60/338 (17.8%)*a	53/209 (*25.4%)*b	55/478 (11.5%)*b,*c
Sensory impairment below a certain level	36/59 (61.0%)*a, *e	86/324 (26.5%)*a, *f	127/198 (64.1%)*b,*f	158/455 (34.7%)*b, *b
Sphincter disturbance	44/64 (68.8%)*e	182/340 (53.5%)*d,*f	155/213 (72.8%)*b,*f	192/483 (39.8%)*b, *d, *c
Severe motor disability at the time of last examination#	24/58 (41.4%)*a, *e	48/326 (14.7%)*a,*f	57/203 (28.1%)*b,*f	42/455 (9.2%)*b, *c
Secondary progression	12/64 (18.8%)*k	63/341 (18.5%)*d,*l	21/213 (9.9%)*l	39/491 (7.9)*d,*k
Cerebrospinal • uid • ndings				
Marked pleocytosis (• 50 WBC/mm^3) or neutrophilia (• 5 neutrophils/mm^3)	5/53 (9.4%)	10/311 (3.2%)*f	35/184 (19.0%)*b,*f	20/420 (4.8%)
Increased IgG index	17/38 (44.7%)	146/220 (66.4%)*d,*f	42/109 (38.5%)*f	101/221 (45.7%)*d

#: Chair-bound or worse, EDSS = expanded disability status scale of Kurtzke; Gd = gadolimium; LESCLs = longitudinally extensive spinal cord lesions extending 3 or more vertebral segments; N.S. = not signi• cant.

*a: Pb0.01 (LESCLsb+NBarkhof Brain MRI lesions b+Nvs. LESCLsb• NBarkhof Brain MRI lesions b+N), *b: Pb0.01 (LESCLsb+NBarkhof Brain MRI lesions b• N vs. LESCLsb• NBarkhof Brain MRI lesions b+N),*c: Pb0.01 (LESCLsb+NBarkhof Brain MRI lesions b+N vs. LESCLsb+NBarkhof Brain MRI lesions b• N), *d: Pb0.01 (LESCLsb• NBarkhof Brain MRI lesions b+N vs. LESCLsb• NBarkhof Brain MRI lesions b• N),*e: Pb0.01 (LESCLsb+NBarkhof Brain MRI lesions b+N vs. LESCLsb• NBarkhof Brain MRI lesions b• N),*f: Pb0.01 (LESCLsb• NBarkhof Brain MRI lesions b+N vs. LESCLsb+NBarkhof Brain MRI lesions b• N), *g: 0.01• Pb0.05 (LESCLsb+NBarkhof Brain MRI lesions b+N vs. LESCLsb• NBarkhof Brain MRI lesions b+N),*h: 0.01• Pb0.05 ((LESCLsb+NBarkhof Brain MRI lesions b• N vs. LESCLsb• NBarkhof Brain MRI lesions b• N),*i: 0.01• Pb0.05 (LESCLsb+NBarkhof Brain MRI lesions b+N vs. LESCLsb+N Barkhof Brain MRI lesions b• N), *j: 0.01• Pb0.05 (LESCLsb• NBarkhof Brain MRI lesions b+N vs. LESCLsb• NBarkhof Brain MRI lesions b• N),*k: 0.01• Pb0.05 (LESCLsb+NBarkhof Brain MRI lesions b+N vs. LESCLsb• NBarkhof Brain MRI lesions b• N),*l: 0.01• Pb0.05 (LESCLsb• NBarkhof Brain MRI lesions b+N vs. LESCLsb+NBarkhof Brain MRI lesions b• N).

Although occurrence of LESCLs was more frequent in OSMS patients than in CMS patients, LESCLs were also clearly present in a considerable fraction of Japanese CMS patients. Because not all MRI scans were performed in the relapse phase, the frequency of LESCLs in the present study could have been underestimated. There is also some ambiguity attributed to the fact that MRI • lms were not assessed centrally in the present study, which was a nationwide survey using questionnaire sheets and not collecting MRI • lms; however, importantly, the present study disclosed distinctive clinical features associated with MRI • ndings. LESCLs, regardless of OSMS or CMS phenotype, were related to greater female preponderance, higher EDSS scores and higher frequencies of bilateral visual loss, transverse myelitis and marked CSF pleocytosis and neutrophilia. Even when we compared the demographic features of MS patients with contrast enhancement of spinal cord lesions to focus on the in• ammatory types of the lesions, we found practically the same tendency as seen for all spinal cord lesions. On the other hand, increased IgG index and secondary progression were more closely associated with the presence of brain lesions ful• lling the Barkhof criteria [14]. In addition, Barkhof brain lesions were more frequently detected in CMS patients than in OSMS patients, whereas negative brain MRIs were more commonly encountered in OSMS patients than in CMS patients, irrespective of the presence of LESCLs.

Therefore, it is reasonable to classify MS patients according to the clinically estimated sites of lesions, as previously reported, and, additionally, into four subgroups based on the presence or absence of LESCLs. Under such a classi• cation system, OSMS patients with LESCLs represent prototypic Asian-type MS, while CMS patients without LESCLs, most of whom have Barkhof brain lesions, represent classical Western-type MS [1]; these two subgroups are supposed to exist at opposite ends of the MS spectrum. CMS patients with LESCLs shared many features with OSMS patients with LESCLs, while there were differences in age at onset, brain lesion loads, CSF IgG response and secondary progression, assigning this subtype a unique position.

Many features were also found to be common between OSMS patients without LESCLs and CMS patients without LESCLs; however, these subtypes differed in terms of age of onset, brain lesion loads, CSF IgG responses and secondary progression. Moreover, the follow-up periods of patients with intermediate phenotypes were similar to those of prototypic ones, excluding the possibility that shortness of observation periods resulted in apparently intermediate phenotypes. Although some researchers have claimed that OSMS patients without LESCLs are in fact in the early course of CMS [23], on the basis of the results of the present study and our own MS series [9,10], OSMS without LESCLs appears to be a unique subtype in Asians.

It is thus suggested that in between the two extreme ends of the MS spectrum, represented by OSMS with LESCLs and CMS without LESCLs, there exist a considerable number of patients with intermediate phenotypes, such as CMS with LESCLs and OSMS without LESCLs, showing similarities and dissimilarities to these prototypes. Solely MRI • nding-based classi• cation also yielded similar results: the Barkhof (+)LESCL(•) group represents Western-type MS and the Barkhof(•)LESCL(+) group represents Asian-type MS, while in between the two exist the Barkhof(+)LESCL(+) and Barkhof(•) LESCL(•) groups. Ikuta et al. [24] investigated a large number of Japanese and American autopsy cases with MS and found OSMS in 47% of the Japanese series, while 13% of the American cases were classi• ed as having OSMS with frequent necrotic lesions pathologically. The results of this study suggest that even in Westerners, cases with OSMS and destructive spinal cord lesions exist with a frequency that should not be ignored.

We recently reported a decrease in peak age at onset in Japanese MS patients over the period of the four nationwide surveys [8]. The present analyses indicate that such "anticipation" of age at onset occurs in patients without LESCLs, irrespective of CMS or OSMS phenotype, but not in those with LESCLs, suggesting that changes in environmental factors associated with modernization may have differentially in• uenced disease susceptibility in each subtype.

In the present survey series, OSMS patients without LESCLs and CMS patients with or without LESCLs all showed a signi• cant positive correlation between disease duration and EDSS scores, while OSMS patients with LESCLs did not. The absence of a correlation between disease duration and EDSS scores in OSMS patients with LESCLs may in part be explained by the fact that the severity of relapses determines the residual disability in anti-AQP4 antibody-positive MS/NMO patients with rare secondary progression [21], who overlap OSMS patients with LESCLs. Future nationwide surveys incorporating anti-AQP4 antibody assays and central assessment of MRI scans in Japanese will give further insight into the mechanisms underlying the phenotypic differences in MS patients.

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Appendix A

The chairmen of the previous nationwide survey committees were Professors Yoshigoro Kuroiwa (Department of Neurology, Kyushu University; • rst survey), Akihiro Igata (Third Department of Internal Medicine, Kagoshima University; second survey), and Hiroshi Nishitani (Department of Neurology, National Utano Hospital; third survey). In the fourth survey, in addition to the authors, the following were members of the Research Committee of Neuroimmunological Diseases: Drs. Susumu Chiba (Department of Neurology, School of Medicine, Sapporo Medical University), Yoshitaka Fujii (Department of Surgery II, Nagoya City University Medical School), Susumu Furukawa (Department of Pediatrics, Yamaguchi University School of Medicine), Hideo Hara (Department of Vascular Dementia Research, National Institute for Longevity Sciences, National Center of Geriatrics and Gerontology), Toshirou Hara (Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University), Kinya Hisanaga (Department of Neurology, Miyagi National Hospital), Shu-ichi Ikeda (Department of Neurology, Shinshu University School of Medicine), Shuji Izumo (Division of Molecular Pathology, Center for Chronic Viral Diseases, Graduate School of Medical and Dental Sciences, Kagoshima University), Ryuji Kaji (Department of Neurology, Graduate School of Medicine, Tokushima University), Takashi Kanda (Department of Neurology and Clinical Neuroscience, Yamaguchi University School of Medicine), Shosei Koh (Department of Biomedical Laboratory Sciences, School of Medicine, Shinshu University), Susumu Kusunoki (Department of Neurology, Kinki University School of Medicine), Satoshi Kuwabara (Department of Neurology, Chiba University School of Medicine), Hidenori Matsuo (Division of Clinical Research, Nagasaki Medical Center of Neurology), Hidehiro Mizusawa (Department of Neurology and Neurological Science, Graduate School, Tokyo Medical and Dental University), Tatsufumi Nakamura (Department of Molecular Microbiology and Immunology, Graduate School of Biomedical Sciences, Nagasaki University), Kyoichi Nomura (Department of Neurology, Saitama Medical School), Mieko Ogino (Department of Internal Medicine III (Neurology), Kitasato University School of Medicine), Yoshiro Ohara (Department of Microbiology, Kanazawa Medical University), Mitsuhiro Osame (Department of Neurology and Geriatrics, Kagoshima University School of Medicine), Kohei Ota (Department of Health Science, Faculty of Science, Tokyo University of Science), Jun Shimizu (Department of Neurology, University of Tokyo), Akio Suzumura (Department of Neuroimmunology, Research Institute of Environmental Medicine, Nagoya University), Takeshi Tabira (Department of

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Appendix B. Supplementary data

Supplementary data associated with this article can befound, in the online version, at doi:10.1016/j.jns.2009.01.008.

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