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Relationship between Barkhof criteria and clinical features of multiple sclerosis in northern Japan

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Running Title: Barkhof criteria in northern Japan

Abstract

Background and Objective We previously reported that the prevalence of MS in Tokachi Province of Hokkaido has increased from 8.6 to 13.1 per 100,000 individuals between 2001 and 2006. Here, we studied the frequency of MS patients who fulfill the Barkhof criteria and identified their common features.

Subjects All 47 subjects in our previous study, who fulfilled Poser's criteria, were included in this study.

Results Of these, 33 satisfied the Barkhof criteria. In 2006, 9.2 per 100,000 MS patients fulfilled the Barkhof criteria; the percentage of patients who fulfilled these criteria was significantly higher among patients born after 1960 than among those born before 1960 (84.3% and 40.0%, respectively). The proportion of patients with conventional MS (C-MS) who fulfilled the Barkhof criteria was higher than that of patients with opticospinal MS (OS-MS) who fulfilled these criteria (93.9% and 71.4%, respectively). Longitudinally extensive spinal cord lesions (LESCLs) were not associated with the brain lesions defined in the Barkhof criteria (Barkhof brain lesions).

Conclusion In Tokachi Province, the increased percentage of MS patients who fulfill the Barkhof criteria was associated with increased C-MS incidence and increase in the proportion of C-MS patients with Barkhof brain lesions among people born after 1960.

Introduction

The 2001 McDonald diagnostic criteria for MS outline the findings of brain MRI that indicate dissemination in space (DIS) and dissemination in time (DIT). In patients with a clinically isolated syndrome (CIS), these 2 phenomena are diagnostic of clinically definite MS (CDMS). In these criteria, typical brain abnormalities seen on MRI are primarily used to diagnose MS [1, 2]. The diagnostic criteria for DIS are based on those recommended by Barkhof *et al.* [3] and Tintoré *et al.* [4]. These criteria are highly accurate for the diagnosis of MS in patients with a CIS in Western countries [3–9], and according to these criteria, at least one of the main clinical features of MS must be present for the diagnosis of DIS. However, few long-term follow-up examinations have been conducted to determine the proportion of MS cases in which the Barkhof criteria are fulfilled [10].

In Japan, MS is generally classified into 2 clinical forms, namely, a conventional form (C-MS) and an opticospinal form (OS-MS) [11, 12]. The latter describes cases in which clinically identified lesions are restricted to the optic nerve and spinal cord and is considered to be the “Asian type,” while the former refers to cases with symptoms involving the brain and is considered to be analogous to MS in Western countries [11, 12]. Some patients with OS-MS have minor brainstem symptoms (e.g., nystagmus and transient double vision) [12], and some of these patients might have an early form of C-MS. Furthermore, MRI criteria for the differentiation between these 2 forms of brain lesions have not yet been established [13]. It has been reported that C-MS in the Japanese population is significantly associated with the HLA-DRB1*1501 allele [12, 14, 15], as is the case in Western countries [16], while OS-MS is associated with the HLA-DPB1*0501 allele [17, 18]. OS-MS might also occur due to lack of the HLA-DPB1*0301 allele [19]. Although the clinical diagnosis of OS-MS is controversial, it has been proposed that OS-MS be considered an independent entity since it shows characteristic clinical signs and is associated with the HLA-DPB1*0501 allele significantly more frequently than C-MS.

We reported the prevalence of MS in Tokachi Province in March 2001 [20] and March 2006 [21]. The incidence of MS increased from 8.6 to 13.1 per 100,000 individuals over these 5 years. The mean annual incidence of MS also increased from 0.15 (1975–1989) to 0.68 (1990–2004) per 100,000 individuals, and this increase was mainly because of the increase in the incidence of C-MS after 1990 [20, 21]. Another study conducted in Japan also reported a marked increase in the proportion of C-MS to OS-MS in patients born after

1960 (4.7:1) [22]. Recent studies conducted in Western countries report that the annual incidence of MS is 3.0–9.2 per 100,000 individuals [23, 24, 25, 26], which is much higher than the incidence in Japan. The proportion of OS-MS in Western patients with MS is much lower than that in the Japanese patients, and the proportion of C-MS is much higher in Western countries than in Japan [27]. The increasing incidence of MS and the progressive predominance of the C-MS phenotype in Japan may reflect the westernization of MS in Japan. However, C-MS in Japan has several characteristics that are different from those observed in Western countries; Japanese patients probably have a lower incidence of cerebellar hemispheric lesions [28] and a higher incidence of longitudinally extensive spinal cord lesions (LESCLs) (14.3–31.5%) [10, 29, 30].

With the recent discovery of the serum anti-aquaporin 4 (AQP4) antibody [31], neuromyelitis optica (NMO) was introduced as a distinct disease entity [32]. In Japan, NMO is differentiated from OS-MS by testing for the serum anti-AQP4 antibody [30, 33]. Although NMO can be associated with brain lesions [34], the differences between NMO in the Asian and Western populations remain largely unknown, and these differences warrant further research.

We estimated the extent of westernization of MS in patients in Tokachi Province on the basis of the incidence of MS and the proportion of the different types of MS. We used the Barkhof criteria to measure the above 2 parameters and discuss the factors influencing the change in the extent of westernization of MS. We also determined the proportion of Japanese patients who satisfied the Barkhof criteria and possessed LESCLs characteristic of Japanese MS. In addition, we examined the influence of the serum anti-AQP4 antibody on the incidence of brain lesions as defined in the Barkhof criteria (hereafter referred to as Barkhof brain lesions).

Materials and methods

Case ascertainment

This study was conducted in Tokachi Province of Hokkaido, the northernmost island of Japan. The population of this province was 358,439 at the end of March 2006. The subjects of this study were those included in our previously published second epidemiological study conducted from March to May 2006 [21]. This study was approved by the Ethical Committee of Obihiro Kosei General Hospital. Information regarding the clinical features of the subjects was collected from the processing sheets based on medical records, which were used in our previous study. We recorded information of the cases in other institutions with a unified form. The criteria of Poser *et al.* [35] were used for the diagnosis of MS in patients in whom the clinical course of disease was the relapse and remitting (RR) type or the secondary progressive (SP) type. The primary progressive (PP) type was diagnosed using the criteria of Polman *et al.* [2]. On the basis of the distribution of lesions, cases were categorized into 2 types, namely, OS-MS and C-MS. OS-MS was defined as MS in which the clinically identified lesions were restricted to the optic nerve and spinal cord, and C-MS was defined as MS with clinical signs involving the cerebrum, brainstem, or cerebellum [11, 12]. Clinical disability was estimated using Kurtzke's expanded disability status scale (EDSS) [36].

MRI analysis

MRI scans obtained at 1.5, 1.0, or 0.5 Tesla for each subject were used in this study. A set of scans for each subject contained T2-weighted images (T2) or T2-weighted fast-fluid attenuated-inversion recovery images (FLAIR) with axial slices through the brain. The slice thickness was 5–10 mm. Gadolinium enhancement and sagittal slices of FLAIR images were used whenever possible.

The MRI scans were evaluated by 2 of the authors (M. Nakamura and H. Houzen). Hyperintense brain lesions larger than 3 mm in cross-sectional diameter were considered as significant lesions, according to the 2001 McDonald diagnostic criteria for MS [1]. These lesions were classified as infratentorial or supratentorial. The latter were divided into juxtacortical (contiguous with the cortex), periventricular (contiguous with the ventricle), or deep white matter not in contact with the cortex or the ventricle. Barkhof *et al.* [3] have defined 4 criteria for the diagnosis of MS lesions by using MRI: (1) the presence of at least 1 gadolinium-enhancing lesion or 9 T2 hyperintense lesions, (2) the presence of at least 1 infratentorial lesion,

(3) the presence of at least 1 juxtacortical lesion, and (4) the presence of at least 3 periventricular lesions. If the demyelinating lesions fulfilled 3 of the 4 abovementioned criteria, the Barkhof criteria were considered to have been fulfilled [3, 4]. We also noted the presence of ovoid lesions of the corpus callosum. Ovoid lesions were defined as oval-shaped, hyperintense lesions oriented perpendicular to the corpus callosum in sagittal FLAIR images. We considered the spinal cord lesions only for the diagnosis of MS, not as alternatives for the brain lesions for the fulfillment of the Barkhof criteria. LESCLs were defined as the spinal cord lesions extending over 3 contiguous vertebral segments. Long spinal cord lesions that consisted of several short spinal cord lesions involving discrete vertebrae were excluded.

Anti-AQP4 antibody measurement

The serum level of anti-AQP4 antibody in MS patients was measured using an indirect immunofluorescence method reported previously [37]. This method involved the use of HEK-293 cells transfected with an AQP4 expression vector containing a full-length complementary DNA (cDNA) of human AQP4. The serum anti-AQP4 antibody level was measured by one of the authors (K. Tanaka).

Subgroup analysis

In Japan, the ratio of the incidence of OS-MS to that of C-MS among individuals born in the 1960s showed a very steep increase (1:4.67). In contrast, that among individuals born before the 1960s showed a slight increment (1:0.5 to 1:1.7) [22]. No significant changes in this ratio were seen among the cohort of people born after the 1960s, although a mild increase in this ratio was noted [22, 38]. Our second epidemiological survey in Tokachi Province also showed an exceedingly large difference in the C-MS to OS-MS ratio between patients born in the 1950s and those born in the 1960s [21]. Thus, the clinical aspects of Japanese patients with MS have changed to a large extent in the population born after the 1960s. We classified our patients into 2 subgroups: those born before and those born after 1960, and compared the following clinical parameters between these 2 subgroups: gender ratio, age at onset, phenotypic ratio, presence of Barkhof brain lesions, LESCLs, and serum anti-AQP4 antibody.

Statistical analysis

The gender ratio, type of clinical course (RR, SP, or PP), clinically apparent lesion distribution (C-MS and

OS-MS), presence or absence of LESCLs, and presence or absence of Barkhof brain lesions were assessed in all patients. The statistical significance of the differences between the above parameters in the 2 groups (e.g., the number of patients fulfilling or not fulfilling the Barkhof criteria, or the number of patients born before or after 1960) was estimated using Fisher's exact probability test. Age, disease duration, and EDSS scores were calculated as mean \pm SD. The statistical significance of the differences in these parameters between the 2 groups was estimated using the Mann-Whitney *U* test.

Results

In our second study on the prevalence of MS, we obtained information from 47 subjects (35 women and 12 men) with MS at the end of March 2006; 44 of these were diagnosed with CDMS and 3 with laboratory-supported MS (LSMS) [21]. The mean age of the subjects was 41.0 ± 13.1 years, and the mean disease duration was 12.6 ± 10.0 years. RR was the most common clinical course (70.2%), followed by SP (25.5%); PP was observed in only 2 patients (4.3%) [21]. Most patients had C-MS (87.2%); OS-MS was observed in only 6 patients (12.8%). The mean EDSS score was 3.1 ± 3.1 (range, 0–9.5) (Table 1).

For the analysis of the brain lesions, MRI scans obtained from April 2005 to January 2008 were used for 32 of the 47 subjects, and 28 of these 32 subjects underwent MRI after our second epidemiological survey in March 2006. In 15 subjects, the latest scans were obtained before April 2005. At the time of the collection of MRI scans, treatment for the prevention of relapse had been administered to 14 subjects, and 24 subjects had not been given any such treatment. We could not obtain any information about the treatment regimen for the other 9 subjects. Of the 14 subjects who received treatment, interferon β (IFN β)-1b was administered to 11, 3 of whom were also administered a low dose of prednisolone (PSL; 5–15 mg/day). Two subjects were administered only PSL. One subject was treated with PSL and mitoxantrone. Of the 24 subjects not receiving any treatment for the prevention of relapses, 3 had been administered IFN β -1b, but by the time the MRI scans used in this study were obtained, the drug had been withdrawn owing to adverse effects. Of these 24 subjects, 2 had been treated with PSL and 1, with azathioprine. To detect spinal cord lesions, we used the spinal MRI scans that had been taken in all the 47 subjects before March 2006.

The Barkhof criteria were fulfilled in 33 patients (70.2%), and the prevalence of Barkhof brain lesions was 9.2 per 100,000 individuals in Tokachi Province. The mean age of the patients fulfilling the Barkhof criteria was significantly lower than that of the patients not fulfilling the Barkhof criteria (37.0 ± 10.1 years and 49.5 ± 15.2 years, respectively; $P = 0.01$) (Table 2). The mean age at onset was also significantly lower in the patients with Barkhof brain lesions than those without Barkhof brain lesions (24.5 ± 7.7 and 36.9 ± 14.7 , respectively; $P = 0.003$) (Table 2). The incidence of C-MS tended to be higher among the patients fulfilling the Barkhof criteria than among those not fulfilling the Barkhof criteria (93.9% and 71.4%, respectively) (Table 2). The gender ratio, mean disease duration, proportion of each clinical course, and mean EDSS score did not significantly differ between the patients fulfilling the Barkhof criteria and those not

fulfilling these criteria (Table 2).

We analyzed the distribution of brain lesions in 45 cases, according to the each item of Barkhof criteria (Table 3). Although we had information as to whether each case fulfilled the Barkhof criteria in all 47 cases, the analysis of each item of the Barkhof criteria was flawed in 2 cases. Thus, we excluded these 2 cases from this analysis. Most of the cases with Barkhof brain lesions fulfilled the following items of the Barkhof criteria: “at least 9 T2 hyperintense lesions,” “at least 1 juxtacortical lesion,” and “at least 3 periventricular lesions.” Infratentorial lesions and gadolinium-enhancing lesions were detected in a relatively small proportion of the study population with or without Barkhof brain lesions. However, in the case of C-MS, patients with Barkhof brain lesions showed the above 2 types of lesions more frequently than those without Barkhof brain lesions. Sagittal slices of FLAIR images of brain were conducted to detect ovoid lesions of the corpus callosum in 40 cases. These ovoid lesions were more frequent in the case of C-MS than in the case of OS-MS, though the difference was not statistically significant (65.7% and 20%, respectively). The incidence of ovoid lesions was significantly higher among the C-MS patients who had Barkhof brain lesions than among those who did not (80.8% and 22.2%, respectively; $P = 0.003$). 5 C-MS patients with Barkhof brain lesions did not have ovoid lesions of the corpus callosum, and 2 C-MS patients without Barkhof brain lesions had these ovoid lesions. Of 5 OS-MS patients, only 1 had ovoid lesions, and this patient fulfilled the Barkhof criteria. The other 4 patients without ovoid lesions did not fulfill the Barkhof criteria. A few of the study patients had cerebellar hemispheric lesions (8 of 45; 17.8%) (C-MS: 7 of 40, 17.5%; OS-MS: 1 of 5, 20.0%).

We determined the proportion of patients with Barkhof brain lesions and categorized our subjects into 2 subclasses on the basis of their birth year (born before or after 1960). The proportion of patients fulfilling the Barkhof criteria was significantly higher among the subjects born after 1960 than among the subjects born before 1960 (27 of 32 patients, 84.3% and 6 of 15 patients, 40.0%, respectively; $P = 0.003$) (Figure 1). Barkhof brain lesions were more common among patients with C-MS. The proportion of C-MS patients who fulfilled the Barkhof criteria was significantly higher among subjects born after 1960 than among those born before 1960 (25 of 29 patients, 86.2% and 6 of 12 patients, 50.0%, respectively; $P = 0.02$) (Figure 1). Barkhof brain lesions were not present in the 3 OS-MS patients who were born before 1960, while 2 of the 3 OS-MS patients born after 1960 fulfilled the Barkhof criteria (Figure 1). In the case of C-MS, the mean age at onset was significantly greater in the subjects born before 1960 than in those born after 1960 (37.6 ± 14.2 years and 23.3 ± 6.5 years, respectively; $P = 0.004$ by Mann-Whitney U test), while not detected

in OS-MS.

LESCLs were detected in 9 patients, of which, 7 had C-MS and 2 had OS-MS. These patients accounted for 17.1% (7 of 41) C-MS patients and 33.3% (2 of 6) OS-MS patients. We studied the relationship between the presence of LESCLs and the fulfillment of the Barkhof criteria among patients with C-MS and OS-MS. Most C-MS patients had Barkhof brain lesions but not LESCLs (61.0%), while very few patients without Barkhof brain lesions had LESCLs (2.4%) (Table 4). The proportion of C-MS patients who fulfilled the Barkhof criteria did not vary with the presence or absence of LESCLs (6 of 7 patients, 85.7% and 25 of 34 patients, 73.5%, respectively) (Table 4). Thus, Barkhof brain lesions can be present even in C-MS patients with LESCLs. In the case of OS-MS, LESCLs were not present in many subjects (2 of 6 subjects; 33.3%), and most patients had neither Barkhof brain lesions nor LESCLs (50.0%) (Table 5).

The serum anti-AQP4 antibody was examined in 29 patients with C-MS and 4 patients with OS-MS; further, of 9 patients with LESCLs (7 C-MS and 2 OS-MS patients), this antibody was examined in 7 (5 C-MS and 2 OS-MS patients). Of the above 33 patients, only 1 (3.0%; female) was positive for the serum anti-AQP4 antibody. She was diagnosed with C-MS; she had LESCLs and fulfilled the Barkhof criteria. None of the OS-MS patients were positive for serum anti-AQP4 antibody.

Discussion

In our previous 2 studies, we showed that the prevalence of MS in Tokachi Province was the highest in East Asia and has been increasing in the past 5 years [20, 21]. In the current study, we focused on the brain MRI data of the subjects included in our previous study [21]. The main findings of this study are as follows:

- (i) A relatively high proportion (70.2%) of the subjects in Tokachi Province fulfilled the Barkhof criteria in March 2006.
- (ii) Barkhof brain lesions and ovoid lesions of the corpus callosum were considerably more frequent among C-MS patients than among OS-MS patients.
- (iii) Cerebellar hemispheric lesions were rare in both C-MS and OS-MS patients.
- (iv) The incidence of Barkhof brain lesions was higher among the C-MS patients born after 1960 than among those born before 1960.
- (v) The incidence of Barkhof brain lesions among C-MS patients was independent of the presence of LESCLs.
- (vi) The most common lesion pattern among C-MS patients was the presence of Barkhof brain lesions but not LESCLs.
- (vii) The presence of serum anti-AQP4 antibody was rare in Tokachi Province.

The brain and spinal cord MRI data used in this study were not obtained under uniform conditions, for example, different magnetic strengths (0.5, 1.0, and 1.5 Tesla) during MRI. This drawback might have led to the underestimation of the number of brain lesions on MRI. We might have also overlooked some ovoid lesions since we could not examine sagittal FLAIR images in all patients. Furthermore, the small number of patients in our study, particularly those with OS-MS, might limit the sensitivity of clinical differences. Therefore, a more extensive study is needed in the future.

The Barkhof criteria were proposed to predict the conversion of CISs to CDMS [3, 4], and in Japan, we found only 1 article (from Kyushu, in the southern part of Japan) describing the proportion of patients with CDMS who were found to fulfill the Barkhof criteria during a long-term follow-up [10]. In their study of 136 subjects with C-MS, OS-MS, or PP type of MS [10], 52.9% fulfilled the Barkhof criteria. This percentage is much lower than that in our study (70.2%). They also reported that the Barkhof criteria are fulfilled in a

considerably greater proportion of C-MS patients (73.1%) than OS-MS patients (24.6%) [10]; this trend is similar to that observed in our study. The most significant difference between our study and the reported study [10] is the C-MS:OS-MS ratio among the study subjects (6.83 and 1.18, respectively), and this difference might account for the difference in the percentage of patients fulfilling the Barkhof criteria. In Japan, the prevalence of OS-MS might not differ greatly between the southern and northern islands [39]. In contrast to the north-south gradient of total MS prevalence in Japan, there is an inverse south-north gradient in the proportion of OS-MS. This gradient is probably an artifact of the north-south gradient in the prevalence of C-MS [39]. Furthermore, the fourth nationwide survey of MS in Japan (2003) also reported that the C-MS:OS-MS ratio and the percentage of MS cases with Barkhof brain lesions were significantly higher in the northern part than in the southern part of Japan and that these ratios are increasing all over Japan [38].

A study conducted in a Western country reported that 67.3% of patients with CDMS fulfilled the Barkhof criteria, as assessed using MRI scans obtained within 6 months of diagnosis [9]. We could not find any other clear description of the proportion of CDMS patients with Barkhof brain lesions in Western countries, although some studies have reported that the proportion of patients with a CIS and Barkhof brain lesions at the onset who converted to CDMS for short periods (1–3 years) was 49–71% [5–7]. In these studies, many patients with CDMS were presumed to fulfill the Barkhof criteria at the time of the survey, despite the subjects being in an early phase of the disease. Considering that our survey was conducted in a longer follow-up period, the proportion of patients with CDMS and Barkhof brain lesions in our study might be lower than that in Western countries. However, we found a close correlation between the fulfillment of the Barkhof MRI criteria and the presence of clinical features indicative of C-MS, suggesting that they are applicable in the diagnosis of this form of MS in Japanese populations, as the same in the diagnosis of MS in Western countries. On the other hand, in the case of OS-MS, the above association was weaker; therefore, these MRI criteria may be less sensitive when used for the diagnosis of this type of MS.

Most of the C-MS patients had cerebral lesions characteristic of Western MS, while the OS-MS patients tended to not have these lesions. We consider that this reflects the difference in the genetic backgrounds of the patients with C-MS and OS-MS, and that these 2 types of MS could be genetically classified into different entities [12, 14, 15, 17, 18, 19]. However, the fact that some OS-MS patients exhibit cerebral lesions typical of Western MS indicates the diversity in the clinical presentations of OS-MS [10, 13]. Furthermore, like the C-MS patients in Japan, some OS-MS patients respond to IFN β -1b, which is

administered for the prevention of relapses [41]. These observations suggest the existence of a subgroup of OS-MS patients who share the genetic background of C-MS patients; thus, these OS-MS patients exhibit clinical characteristics that are similar to those of C-MS due to some environmental factors. We consider that OS-MS and C-MS might form a continuous clinical spectrum, as reported in another article [10], and that Barkhof brain lesions might be present in a subgroup of OS-MS patients.

Cerebellar hemispheric lesions were rarely observed in this study (17.8% in 45 patients), regardless of the clinical phenotypes. A study conducted on 66 Japanese patients with MS from Tohoku Province reported that patients with cerebellar hemispheric lesions accounted for only 6.4% of the study population [28]. The low incidence of cerebellar hemispheric lesions is presumably a feature of MS in Japanese people.

In this study, the proportion of patients fulfilling the Barkhof criteria was significantly greater among those born after 1960 than among those born before 1960. This increase may be attributed in part to the increase in the proportion of patients with C-MS among the total number of patients with MS among individuals born after 1960. An increase in the incidence of C-MS has also been observed in Kyushu [22], and recently, this trend was reported to occur throughout Japan, as determined by the fourth nationwide survey [38]. Moreover, patients with C-MS born after 1960 fulfilled Barkhof criteria more frequently than those with C-MS born before 1960 in this study. We consider this phenomenon is more strongly associated with the increase of MS patients with Barkhof brain lesions among those born after 1960. We also found that in the case of C-MS, the age at onset was higher among subjects born before 1960 than among those born after 1960. This trend was not observed among the OS-MS patients. The lower age at onset might be associated with the higher rate of fulfillment of the Barkhof criteria among C-MS patients born after 1960. These changes in number and nature of the Japanese patients with MS could be a result of the westernization of the Japanese environment along with the rapid economic growth that began in the 1960s [22].

In Western countries, MS patients typically exhibit multiple spinal cord lesions that involve less than 2 contiguous vertebral segments [42, 43]. One study reported that only 3 of 68 (4.4%) patients with CDMS and clinically probable MS, which were independently diagnosed before the introduction of the Poser criteria, had spinal cord lesions involving >3 contiguous vertebral segments [42]. Another study reported the high incidence of long spinal cord lesions in Western countries (14 of 91 MS patients; 15.3%) [43]. However, the above study included a large number of patients with PP type of MS (31 of 91 cases), and most patients with long spinal cord lesions had the PP type of MS (10 of 14 patients), which is not considered to be typical

MS. Another study found that within 6 months of diagnosis, 13 of 104 patients with CDMS or LSMS (12.5%) developed diffuse spinal cord lesions, with a mean length of 11.2 ± 5.7 vertebral segments [9]. The incidence of LESCLs among the C-MS patients (17.1%) in our study is higher than that observed in Western countries. In our study, most of the C-MS patients with LESCLs fulfilled the Barkhof criteria. In Japan, no significant difference has been reported in the length of the spinal cord lesions between C-MS and OS-MS patients [12]. Furthermore, some recent studies conducted in Japan have shown that many C-MS patients exhibit LESCLs (14.3–31.5%) [10, 29, 30] and that many of these patients fulfilled the Barkhof criteria (85.0–88.2%) [10, 30]. The trend that some C-MS patients have both LESCLs and Barkhof brain lesions could be considered to be one of the characteristic features of Japanese C-MS patients.

We detected serum anti-AQP4 antibody in only 1 patient. This patient had C-MS with LESCLs; none of the OS-MS patients tested positive for serum anti-AQP4 antibody. The percentage of patients with serum anti-AQP4 antibodies has been reported to be 14.2% (16 of 113 consecutive patients with CDMS) in Kyushu Province [30], and the percentage of patients with serum NMO- IgG, which is similar to the serum anti-AQP4 antibody, has been reported to be 40% (14 of 35 patients with CDMS) in Tohoku Province [33]. The prevalence of the serum anti-AQP4 antibody in Tokachi Province (3.0 %) was lower than the prevalence rates reported in the abovementioned 2 studies. The population in this study is based on an epidemiological study in Tokachi Province, and we suppose our data could reflect relatively precise prevalence of patients with serum anti-AQP4 antibody in northern Japan. A more extensive study is required to clarify the relationship between the Barkhof criteria and anti-AQP4 antibody.

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Figure legend

Figure 1

A total of 47 patients with MS were categorized into 2 subclasses according to birth year (before or after 1960). Next, the patients in each subclass were further divided into those who had C-MS and fulfilled the Barkhof criteria, those who had C-MS but did not fulfill the Barkhof criteria, those who had OS-MS and fulfilled the Barkhof criteria, and those who had OS-MS but did not fulfill the Barkhof criteria. The proportion of patients fulfilling the Barkhof criteria was significantly higher among subjects born after 1960 than among those born before 1960 (27 of 32 patients, 84.4% and 6 of 15 patients, 40.0%, respectively; $P = 0.003$). Of the 32 patients (90.6%) born after 1960, C-MS was present in 29, and 25 of these 29 patients (86.2%) fulfilled the Barkhof criteria. In contrast, C-MS was present in 12 of the 15 patients (80.0%) born before 1960, and 6 of these 12 patients (50.0%) fulfilled the Barkhof criteria. The proportion of C-MS patients who fulfilled the Barkhof criteria was significantly higher among the subjects born after 1960 than among those born before 1960 (25 of 29 patients and 6 of 12 patients, respectively; $P = 0.02$). The increase in the number of patients with Barkhof brain lesions may be attributable in part to the increase in the number of C-MS patients and mainly to the increase in the proportion of C-MS patients born after 1960 who fulfill the Barkhof criteria.

Table 1 Clinical features of the patients included in this study

Female/Male	35/12
Mean age (years) \pm SD (range)	41.0 \pm 13.1 (15–80)
Mean age at onset (years) \pm SD (range)	28.4 \pm 11.7 (7–60)
Mean disease duration (years) \pm SD (range)	12.6 \pm 10.0 (2–48)
RRMS/SPMS/PPMS	33 (70.2%)/12 (25.5%)/2 (4.3%)
C-MS/OS-MS	41 (87.2%)/6 (12.8%)
Mean EDSS \pm SD (range)	3.1 \pm 3.1 (0–9.5)

RRMS: relapsing-remitting type multiple sclerosis, SPMS: secondary progressive type multiple sclerosis, PPMS: primary progressive type multiple sclerosis,

C-MS: conventional multiple sclerosis, OS-MS: opticospinal multiple sclerosis, EDSS: Kurtzke's expanded disability scale

Table 2 Comparison of clinical features between cases fulfilling and not fulfilling Barkhof criteria

	Barkhof (+) (n = 33)	Barkhof (-) (n = 14)
Female/Male	26 (78.8%)/7 (21.2%)	9 (64.3%)/5 (35.7%)
Mean age (years) \pm SD (range)*	37.0 \pm 10.1 (15–59)	49.5 \pm 15.2 (23–80)
Mean onset age (years) \pm SD (range)**	24.5 \pm 7.7 (12–48)	36.9 \pm 14.7 (7–60)
Mean disease duration \pm SD (range)	12.5 \pm 9.3 (2–40)	12.6 \pm 11.1 (2–48)
RRMS/SPMS/PPMS	23 (69.7%)/8 (24.2%)/2 (6.1%)	10 (71.4%)/4 (28.6%)/0 (0.0%)
C-MS/OS-MS	31 (93.9%)/2 (6.1%)	10 (71.4%)/4 (28.6%)
Mean EDSS \pm SD (range)	2.9 \pm 3.0 (0–9.5)	3.6 \pm 3.2 (0–9)

Barkhof (+): cases fulfilling Barkhof criteria, Barkhof (-): cases not fulfilling Barkhof criteria, other abbreviations are as defined in Table 1

* $P = 0.01$, by Mann-Whitney U test, for difference between Barkhof (+) cases and Barkhof (-) cases

** $P = 0.003$, by Mann-Whitney U test, for difference between Barkhof (+) cases and Barkhof (-) cases

Table 3 Lesion distribution in Brain MRI of our cases

Lesions	Barkhof (+) (n=32) [C-MS (n=30) : OS-MS (n=2)]	Barkhof (-) (n=13) [C-MS (n=10) : OS-MS (n=3)]
Nine T2 hyperintense lesions	32/32 (100%) [30/30 (100%) : 2/2 (100%)]	4/13 (30.8%) [3/10 (30.0%) : 1/3 (33.3%)]
One gadolinium-enhancing lesion*	8/27 (29.6%) [8/25 (32.0%) : 0/2 (0%)]	0/9 (0%) [0/6 (0%) : 0/3 (0%)]
One infratentorial lesion	16/32 (50.0%) [16/30 (53.3%) : 0/2 (0%)]	3/13 (23.1%) [2/10 (20.0%) : 1/3 (33.3%)]
One juxtacortical lesion	32/32 (100%) [30/30 (100%) : 2/2 (100%)]	8/13 (61.5%) [6/10 (60.0%) : 2/3 (66.7%)]
Three periventricular lesions	31/32 (96.9%) [29/30 (96.7%) : 2/2 (100%)]	2/13 (15.4%) [2/10 (20.0%) : 0/3 (0%)]
Ovoid lesions**	22/28 (78.6%) [21/26 [†] (80.8%) : 1/2 (50.0%)]	2/12 (16.7%) [2/9 [†] (22.2%) : 0/3 (0.0%)]
Cerebellar hemispheric lesions	6/32 (18.8%) [6/30 (20.0%) : 0/2 (0.0%)]	2/13 (15.4%) [1/10 (10.0%) : 1/3 (33.3%)]

The objects were limited to 45 of 47 cases for this analysis (see Materials and Methods).

* The gadolinium enhancing was conducted for 36 of 45 cases at analysis.

** The ovoid lesions of corpus callosum were examined in 40 of 45 cases.

[†]P=0.003, by Fisher's exact probability test, for difference between C-MS with Barkhof brain lesions and C-MS without Barkhof brain lesions in the rate of the cases with ovoid lesions of the corpus callosum

Table 4 Relationship between LESCLs and Barkhof criteria in C-MS

C-MS (n = 41)	Barkhof	
	(+)	(-)
LESCLs		
(+)	6 (14.6%)	1 (2.4%)
(-)	25 (61.0%)	9 (22.0%)

Table 5 Relationship between LESCLs and Barkhof criteria in OS-MS

OS-MS (n = 6)	Barkhof	
	(+)	(-)
LESCLs		
(+)	1 (16.7%)	1 (16.7%)
(-)	1 (16.7%)	3 (50.0%)

Figure 1

