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# Heterogeneity and continuum of multiple sclerosis in Japanese according to magnetic resonance imaging findings

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**Abstract**

There are two distinct subtypes of multiple sclerosis (MS) in Asians: optic-spinal (OSMS) and conventional (CMS). Longitudinally extensive spinal cord lesions (LESCLs) extending over three or more vertebral segments are characteristic of patients with OSMS, yet in Asians, one-fourth of CMS patients also have LESCLs. To clarify the distinction between LESCLs in OSMS and CMS, and to characterize the relationship between the presence of LESCLs and brain magnetic resonance imaging (MRI) findings, we studied 142 patients with clinically definite MS of relapsing–remitting onset and 12 patients with primary progressive MS (PPMS) by MRI of the whole spinal cord and brain. The former was diagnosed by Poser criteria, including 57 with OSMS, 67 with CMS and 18 with brainstem-spinal form of MS, while the latter by McDonald criteria. The presence of LESCLs throughout the entire clinical course was significantly more common in OSMS patients than in CMS patients, while brain lesions fulfilling the Barkhof criteria (Barkhof brain lesions) were significantly more common in CMS patients than OSMS patients. LESCLs in OSMS patients most frequently affected the upper to middle thoracic cord, with either holocord or central gray matter involvement. By contrast, 70% of LESCLs in CMS patients predominantly affected the peripheral white matter of the mid-cervical cord. LESCLs in patients with PPMS also showed preferential involvement of the peripheral white matter of the mid-cervical cord. One-third of OSMS patients had neither LESCLs nor Barkhof brain lesions more than 10 years after disease onset, and showed significantly milder disability than OSMS patients with LESCLs. These findings suggest that LESCLs are heterogeneous between OSMS and CMS patients, and that there are distinct subtypes of MS in Japanese, according to clinical and MRI findings.


*Keywords:* Multiple sclerosis; Magnetic resonance imaging; Optic-spinal form; Neuromyelitis optica; Spinal cord; Japanese; Conventional form

## 1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). It has been hypothesized to be caused by an autoimmune mechanism targeting CNS myelin. MS is rare in Asians, but when it does appear, the destruction of the optic nerves and spinal cord is striking [1].

We previously reported the existence of two subtypes of MS in Japanese: the optic-spinal form (OSMS), which shows selective and severe involvement of the optic nerves and spinal cord, and the conventional form (CMS), which shows disseminated lesions in the CNS including the cerebrum, cerebellum and brainstem [2]. The two subtypes have different clinical and neuroimaging features, and immunogenetic backgrounds [1–3]. OSMS is characterized by a greater age at onset, marked female preponderance and a higher Kurtzke's Expanded Disability Status Scale (EDSS) score [4], resulting from severe visual impairment and marked spinal cord dysfunction, compared with CMS. In patients with OSMS, long, swollen spinal cord lesions extending over three or more vertebral segments are common on magnetic resonance imaging (MRI) [1]. The presence of such

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longitudinally extensive spinal cord lesions (LESCLs), as well as the occasionally higher cell counts and amounts of protein in the cerebrospinal fluid (CSF), suggest severe inflammatory destruction in OSMS patients. Furthermore, pathological studies have revealed not only demyelination, but also axonal loss, necrosis, cavity formation, thickened vessel walls and capillary proliferation, in OSMS lesions [5–7].

In Western MS series, spinal cord lesions are usually less than two vertebral segments long and occupy less than one-half of a spinal cross-section, preferentially involving the peripheral white matter [8]. However, we previously reported that LESCLs extending over three or more vertebral segments were found significantly more frequently in OSMS patients than CMS patients, while one-fourth of Japanese patients with CMS also had LESCLs [9], reflecting the severe spinal cord damage commonly seen in Asians. Although the frequency of LESCLs in Asian MS patients has been reported by us [9,10] and others [11,12], and the heterogeneity of LESCLs from the point of view of anti-aquaporin 4 antibody status has recently been described by us [13], the fine distribution of LESCLs in the spinal cord, in the sagittal and axial planes, has not been extensively studied in each clinical phenotype, including primary progressive MS (PPMS). On the other hand, brain lesions fulfilling the Barkhof criteria (Barkhof brain lesions) [14] are less common in Asians, especially in patients with OSMS [9].

Thus, at present, the heterogeneity of LESCLs in MS subtypes is uncertain. In the present study, we attempted to determine the heterogeneity of LESCLs in each MS subtype by extensively studying the MRI features of spinal cord lesions in a large series of Japanese MS patients. In addition, we further characterized the relationship between the presence of LESCLs and brain MRI findings.

## 2. Materials and methods

### 2.1. Subjects

According to the criteria of Poser et al. [15], 142 consecutive patients, including 36 males and 106 females, were diagnosed with clinically definite MS (CDMS) of relapsing–remitting onset, while the 12 with PPMS were diagnosed on the basis of the McDonald criteria [16]. They were subjected to brain and whole spinal cord MRI at the MS clinic in the Department of Neurology, Kyushu University Hospital, between 1987 and 2006. All patients underwent a thorough neurological examination and routine laboratory tests. All were followed-up and clinically evaluated at regular intervals in the MS clinic. Their medical records and MRI films were analyzed retrospectively for the present study. All of the patients were residents of Kyushu Island, the southern-most part of mainland Japan. None of the patients was seropositive for human T-cell leukemia virus type I. Patients with monophasic neuromyelitis optica (NMO) without subsequent relapse were excluded, to avoid including patients with acute disseminated encephalomyelitis. Their age at onset was 32.4±14.0 years (mean±S.D.), and disease duration was 9.9±9.4 years.

The CDMS patients with relapsing–remitting onset were clinically classified into two subtypes, OSMS and CMS, as described previously [2]. Briefly, patients who had a relapsing–remitting course and both optic nerve and spinal cord involvement, without any clinical evidence of disease in either the cerebrum or the cerebellum, were considered to have OSMS. Patients with minor brainstem signs, such as transient double vision and nystagmus, in addition to optic-spinal involvement, were included in this subtype. Patients with multiple involvement of the CNS, including the cerebrum and cerebellum, were considered to have CMS. Accordingly, 57 patients were classified as having OSMS, and 67 as CMS. Eighteen patients with only brainstem and spinal cord symptomatology were difficult to classify into either subtype, and were temporarily grouped together under the term brainstem-spinal form of MS (BSMS). The disability status of the patients was scored by one of the authors (J.K.) throughout the study, according to the EDSS [4]. The average EDSS score of all of the MS patients was 4.2±2.5. Severe optic neuritis was defined as grade 5 or more than 5 on Kurtzke's Visual Functional Scale (FS) [4]. Acute transverse myelitis (ATM) was defined according to Fukazawa et al. [17].

### 2.2. Magnetic resonance imaging

All MRI studies were performed using 1.5 T MRI units, (Magnetom Vision and Symphony; Siemens Medical Systems, Erlangen, Germany), as described previously [9]. The typical imaging parameters for the brain were as follows: axial T2-weighted turbo spin-echo imaging using TR/TE=2800/90 ms, flip angle=180°; axial turbo-fluid-attenuated inversion recovery (FLAIR) imaging using TI/TR/TE=2200/9000/110 ms, flip angle=180°; and sagittal and axial pre-contrast and axial and coronal post-contrast T1-weighted spin-echo imaging using TR/TE range=400–460/12–17 ms, flip angle range=80–90°. One excitation, with a matrix of 256×256 (pixel size=0.90×0.90 mm), slice thickness of 5 mm, and a slice gap of 2.5 mm, was used for all brain studies. Gadopentetate dimeglumine, at a concentration of 0.1 mmol/kg body weight, was administered intravenously for contrast-enhanced studies. The typical imaging parameters for the spinal cord were as follows: sagittal T2-weighted turbo spin-echo imaging using TR/TE range=2500–2800/90–116 ms, flip angle=180°, number of excitations=3 or 4; sagittal T1-weighted spin-echo imaging using TR/TE range=400–440/11–12 ms, flip angle range=90–170°, number of excitations=2 or 3; axial T2-weighted turbo spin-echo imaging using TR/TE range=3200–5360/99–116 ms, flip angle=180°, number of excitations=3 or 4; and axial T1-weighted spin-echo imaging using TR/TE range=400–440/12 ms, flip angle range=90–170°, number of excitations=2. For sagittal imaging, a matrix of 256×256