Comparison of the Clinical Courses of the Opticospinal and Conventional Forms of Multiple Sclerosis in Japan

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Abstract

We evaluated the clinical courses of 216 patients with multiple sclerosis (MS) diagnosed according to the recommended diagnostic criteria of McDonald et al (10). Sixty-five patients clinically displaying selective involvement of the optic nerves and spinal cord were classified as opticospinal MS (OS-MS), while the other 151 showing disseminated involvement of the central nervous system were classified as conventional MS (C-MS). The disease duration did not differ significantly between the two subtypes (11.2 years vs. 11.5 years). In addition to a higher age of onset, female preponderance and higher Kurtzke’s expanded disability status scale (EDSS) scores, the OS-MS patients showed a markedly lower frequency of secondary progressive MS than the C-MS patients (4.6% vs. 29.1%, p=0.0001). The EDSS scores of the C-MS patients were significantly correlated with the disease duration, while those of the OS-MS patients were not. Among the C-MS patients, the frequency of secondary progressive MS was significantly more common in patients with a disease duration of more than 10 years than in those with a shorter duration. These results suggest that the irreversible disability in OS-MS is determined by relapses, rather than by chronic progression, whereas C-MS has a similar clinical course to MS in Westerners.

Key words: multiple sclerosis, opticospinal form, conventional form, progression

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of unknown etiology, and an increasing amount of evidence suggests that it is heterogeneous. According to its clinical course, MS can be described as relapsing-remitting type (RR-MS), secondary progressive type (SP-MS), in which a progressive phase follows an initial relapsing-remitting phase, or primary progressive type (PP-MS), in which the disease shows a progressive course from its onset. On the other hand, concerning the sites of involvement, there have been several reports that Oriental MS patients more commonly show clinical evidence of major involvement of the optic nerves and spinal cord than Caucasian MS patients (1). In addition, we previously reported the clinical and immunogenetic characteristics of two further MS subtypes in Japanese populations, namely opticospinal MS (OS-MS), in which the clinically estimated main lesions are confined to the optic nerves and spinal cord, and conventional MS (C-MS), which shows disseminated lesions in the central nervous system (CNS), including the cerebrum, cerebellum or brainstem (2–4). OS-MS has distinct features, such as marked female preponderance, higher age at onset, higher Kurtzke’s expanded disability status scale (EDSS) scores (5) resulting from severe visual impairment and marked spinal cord dysfunction, and a lower number of brain lesions on magnetic resonance imaging (MRI) compared with C-MS (6). Severe inflammatory destruction is indicated in OS-MS by the higher cell counts and increased amounts of protein in the cerebrospinal fluid (CSF), and the long swollen lesions extending over several vertebral segments on spinal cord MRIs (6). Pathological studies have also revealed severe inflammation and vascular changes in OS-MS lesions (7, 8).

OS-MS is relatively common among Asians compared...
with Westerners, while early studies indicated that the progressive type is rare among Japanese MS patients (9). However, in these studies, the follow-up periods and disease durations were not sufficient and the number of MS patients was not large enough to determine the clinical course of Asian MS. Moreover, the clinical courses have not been compared between each clinical subtype in Asian MS patients. In the present study, we therefore studied the clinical courses of large numbers of MS patients with an average disease duration of more than 10 years according to each clinical subtype, and found that OS-MS and C-MS showed distinct clinical courses.

Patients and Methods

A total of 216 patients (56 males and 160 females) with MS diagnosed according to the recommended diagnostic criteria of McDonald et al (10) were recruited from the Department of Neurology, Kyushu University Hospital, the Department of Neurology, Hokkaido University Hospital, and Hokuyukai Neurological Hospital between August 1989 and November 2001. They represented consecutive patients who gave consent in accordance with the declaration of Helsinki. Hematological and biochemical studies and serologic tests for syphilis were performed in all patients. No patients were seropositive for human T-cell leukemia virus type 1. The mean ages at examination and disease onset were 41.5±13.0 years (mean±SD) and 30.1±12.0 years, respectively, and the mean disease duration was 11.4±8.7 years. After at least 1 year of observation, 169 of the patients were diagnosed as RR-MS, and 47 were diagnosed as SP-MS, in which the onset of a progressive disease was defined as continual worsening of the symptoms and signs over a period of at least 6 months, with or without superimposed relapses (10, 11). PP-MS patients were not included in the present study because their number was too small for statistical analysis. The MS severity was evaluated by Kurtzke’s EDSS scores (5). The medical records of all the patients were reviewed retrospectively. Overall, the frequency of SP-MS was 21.8% (47/216), and the mean EDSS score at the time of examination was 3.8±2.6.

In the present study, the MS patients were classified into the two clinical subtypes. The patients whose clinically estimated lesions were confined to the optic nerves and spinal cord were classified as OS-MS. These patients showed no clinical evidence of disease in either the cerebrum or cerebellum, and those with minor brainstem signs, such as transient double vision and nystagmus, in addition to the opticospinal involvement were included. In Japan, Devic disease is diagnosed for cases with a monophasic course and, since such monophasic cases potentially contain acute disseminated encephalomyelitis cases, patients with Devic disease were excluded. Recurrent optic neuritis and recurrent transverse myelitis involving the identical level were also excluded from OS-MS. The remaining MS patients, who showed the involvement of multiple sites in the CNS, including the cerebrum, cerebellum or brainstem, were classified as C-MS. This study was approved by the Ethical Committee of the Institution in which it was performed.

Statistical analyses of the clinical parameters between OS-MS and C-MS were performed, using the Mann-Whitney U-test and chi-square test. Spearman’s correlation was used for statistical analyses of the disease duration and EDSS scores. Values of p<0.05 were considered statistically significant. Statistical analyses were performed with StatView/Windows software.

Results

Comparisons of the clinical findings of OS-MS and C-MS

The proportion of females was significantly higher in OS-MS than in C-MS (1 : 6.2 vs. 1 : 2.2, p=0.0079) (Fig. 1). The age at disease onset was significantly higher in OS-MS than in C-MS (38.1±13.9 years vs. 26.7±9.2 years, p<0.0001), while the disease duration did not differ significantly (11.2±8.6 years vs. 11.5±8.8 years). The EDSS scores were significantly greater in OS-MS than in C-MS (4.8±2.3 vs. 3.5±2.7, p=0.0004).

Comparisons of the clinical courses of OS-MS and C-MS

In OS-MS, 62 patients were RR-MS and 3 were SP-MS, while in C-MS, 107 patients were RR-MS and 44 were SP-MS. The frequency of SP-MS was significantly lower in OS-MS than in C-MS (4.6% vs. 29.1%, p=0.0001) (Fig. 1). When the frequency of SP-MS was compared among C-MS patients with long (>10 years) and short (<10 years) disease durations, the frequency was significantly higher in the former (45.7% vs. 14.8%, p<0.0001) (Fig. 2). Among the C-MS patients, SP-MS was also significantly more common in those with moderate to severe disabilities (EDSS ≥4) than in those with mild disabilities (EDSS <4) (73.6% vs. 3.1%, p<0.0001). The EDSS scores of the C-MS patients were significantly correlated with the disease duration (r=0.415, p<0.0001), while those of the OS-MS patients were not (r=0.185, p>0.1) (Fig. 3). When the proportions of patients with moderate to severe disabilities, that is, those with an EDSS score of 4 (limited walking ability) or more, were compared in each tertile of disease duration (<10 years, 10–20 years and ≥20 years), the OS-MS patients showed a significantly higher frequency of moderate to severe disabilities in the lower tertile than the C-MS patients (55.9 vs. 17.3%, p<0.0001), while the other tertiles did not differ (Fig. 4).

Comparisons of the clinical findings between Kyushu and Hokkaido cases

The proportion of OS-MS was significantly higher in Kyushu cases than in Hokkaido cases (OS-MS : C-MS, 1.0 : 1.0 vs. 1.0 : 4.0, p<0.0001). Reflecting the higher population of OS-MS in the Kyushu cases, the frequency of SP-MS was significantly lower in Kyushu cases than in
The age at disease onset was also significantly higher in Kyushu cases than in Hokkaido cases (33.3±12.4 years vs. 28.6±11.5 years, p=0.0093). However, other than these points, there were no statistically significant differences in other clinical parameters between the Kyushu and Hokkaido cases.

**Discussion**

In the present study, we focused on comparing the clinical courses of OS-MS and C-MS by retrospectively analyzing large numbers of MS patients. The results revealed that SP-MS is significantly more uncommon in OS-MS than in C-MS, even at more than 10 years after the disease onset, and that the disability in OS-MS patients is primarily determined by relapses, rather than by chronic progression of the disease.

The retrospective nature of the present study partly limits the validity of the results. In addition, although experienced clinical neuroimmunologists from both institutions used the same evaluation protocols after a consensus was reached, the data collection from two different institutions may have imposed some inter-institutional variation. However, an EDSS score of 4 can easily be determined retrospectively and is frequently adopted in other studies to check disease progression (12). The proportion of OS-MS patients with an EDSS score of 4 was significantly higher than that of C-MS patients within 10 years after the disease onset. It is therefore considered that in the early course of the disease, OS-MS patients experience more moderate to severe disabilities following relapses. A similar trend was reported in African Americans (13). In that report, more African Americans had early pyramidal system involvement than Caucasians, leading to greater EDSS scores, while the rates of disease progression at later stages were nearly identical. Since Africans and their
descendants are known to preferentially show opticospinal involvement (14, 15), it is possible that early deterioration is universally characteristic of OS-MS, regardless of race. Early studies on Asian MS reported that the progressive form was infrequent. For example, Shibasaki et al (9) retrospectively reviewed 204 British and 60 Japanese MS cases and revealed that the progressive phase was observed in 36% of the former but in only 12% of the latter with or without superimposed relapses. However, in that study, the clinical courses were not analyzed according to the MS subtype and the disease duration of the Japanese patients was 8 years on average (9). In the present study, classification into the two subtypes revealed that C-MS frequently showed a secondary progressive disease in the late stage of illness, especially in patients with grave disabilities, and that there was a significant correlation between disease severity and disease duration. On the contrary, secondary progression was significantly less common in OS-MS than in C-MS, yet the disease durations were similar between the two. Moreover, OS-MS showed no relationship between disease severity and disease duration. These observations suggest that the infrequent occurrence of SP-MS in Asians is attributable to the rarity of the secondary progressive phase in OS-MS, and that the disability in OS-MS patients is determined mainly by the severity of relapses, while that in C-MS is determined largely by chronic progression.

A similar retrospective study recently performed on 1,844 MS patients in Western countries with a mean disease duration of 11±10 years revealed that relapses had no significant influence on the progression of irreversible disability (12). This finding therefore indicates that irreversible disabilities are determined by chronic progression in Western MS patients. Based on the results of the present study, the same appears to be true for Japanese C-MS patients. Although earlier studies reported that the progressive phase was rare in Asians(9), the results of the present study demonstrate that, after longer disease durations, a considerable proportion of C-MS patients enter a similar progressive phase, suggesting that identical pathomechanisms are operative in C-MS even in Asians. Therefore, the process of C-MS is considered to be neurodegeneration plus superimposed inflammation similar to Western MS (16), while that of OS-MS is thought to be purely inflammatory.

In summary, the results of the present study indicate that OS-MS is distinct from C-MS in terms of their clinical courses, further suggesting the possibility that distinct mechanisms might be operative. However, once OS-MS patients contract grave disabilities as a result of a severe
relapse, it is difficult to evaluate the chronic progression retrospectively. This may be explained in part by the rarity of SP-MS in OS-MS. Considering the rarity of MS in Japan, it is desirable to create a nationwide prospective study system using the same evaluation scale, such as the EDSS score, in the future.

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References