

## Decrease in Multiple Sclerosis with Acute Transverse Myelitis in Japan

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NAKASHIMA, I., FUJIHARA, K., TAKASE, S. and ITOYAMA, Y. *Decrease in Multiple Sclerosis with Acute Transverse Myelitis in Japan*. Tohoku J. Exp. Med., 1999, 188(1), 89-94 — Acute transverse myelitis (ATM) may be a manifestation of multiple sclerosis (MS) and was reported to be more common among Japanese MS patients than in Caucasian MS patients. Recently there are arguments whether clinical manifestations of MS may have changed. Therefore, we studied the frequency of ATM in MS and the clinical subtypes of MS in 86 clinically definite MS patients whose onsets were in 1970-1979, 1980-1989, and 1990-1998 in Sendai City, Japan. Fifty-six of the patients were women and 30 were men. Forty-four patients had the conventional form of MS (C-MS) commonly seen in Western countries, and 42 had optic-spinal or spinal forms of MS (OSS-MS). Twenty MS patients had ATM, and all of them were belong to optic-spinal form of MS. ATM was not seen in any cases of C-MS. The mean onset age (years) of the clinical subtypes was 25.5 in C-MS, 34.1 in OSS-MS without ATM, and 30.9 in OSS-MS with ATM. Among the patients whose onset of the disease was in 1970-1979, 60.0% of them were cases of OSS-MS with ATM, but such cases were markedly decreased to 5.3% in 1990-1998. In contrast, the frequency of C-MS increased to 63.2% in 1990-1998 compared with 20.0% in 1970-1979. Analysis of the data by the year of birth of the patients showed similar results. Our data suggest that the frequency of ATM in MS markedly decreased, and that of C-MS increased during the last 30 years in Sendai, Japan. Since the genetic background of Japanese has not changed, some exogenous factors, such as food, infectious microorganisms, and chemicals in our environment, may be responsible for the change. ————— multiple sclerosis; acute transverse myelitis; Japanese; optic-spinal form © 1999 Tohoku University Medical Press

Acute transverse myelitis (ATM) may be a manifestation of multiple sclerosis (MS) (Fukazawa et al. 1990; Miller 1996). A comparative analysis of the clinical features in Japanese and British MS patients reported in 1981 showed that ATM was more common in Japanese patients than in Caucasian patients (Shibasaki et

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al. 1981). Recent reports on Caucasian patients suggest that patients of ATM only rarely develop MS (Bakshi et al. 1998; Scott et al. 1998). There is no doubt that some environmental factors are related to the pathomechanisms of MS, and that have been drastic changes in the environment in the last 30–50 years in Japan. Thus, it would be of interest to study whether there have been any recent changes in the clinical manifestations of MS and the frequency of MS subtypes with special reference to ATM in Japan. However, such a study has never been conducted. In the present study, we studied the changes in clinical subtypes of MS patients with special reference to MS with ATM in 1970–1998, 1980–1989, and 1990–1998 in Sendai.

#### PATIENTS AND METHODS

Sendai City is located in the northern part of Japan, and now has a population of about one million. Tohoku University Hospital is the only university hospital in the city, and the majority of MS patients are eventually referred to its Department of Neurology. We retrospectively reviewed the medical records of eighty six Japanese patients with clinically definite MS by Poser's criteria whose onset of MS was in 1970–1979, 1980–1989, and 1990–1998 and were seen at Tohoku University Hospital.

At first, the 86 cases were classified into 2 clinical subtypes based on their clinical symptoms and signs as follows: (1) Conventional form of MS (C-MS), cases with disseminated central nervous system deficits in both time and space. This type of MS is commonly seen in Western countries. (2) Optic-spinal or spinal forms of MS (OSS-MS), which is characterized by recurrent optic neuritis and myelitis without any cerebral, brainstem, or cerebellar symptoms and signs. This type of MS is relatively common in Asian countries, including Japan. The spinal form of MS is characterized by recurrent myelitis without any other CNS symptoms and signs. Then, these cases of OSS-MS were further classified into two groups according to whether they were ATM or non-transverse myelopathy. ATM was defined as acute myelopathy characterized by (a) moderate to severe paraparesis or quadriparesis, (b) pallhypesthesia with a sensory level, and (c) neurogenic bladder. Cases which lack (a), (b) or (c) were defined as non-transverse myelopathy. In this study, the classification of ATM or non-transverse myelopathy was essentially based on the neurological findings because MRI findings were not available from 1970 to the mid-1980s. Devic's disease, which is characterized by the concurrent development of severe bilateral optic neuritis and transverse myelitis, was not found among the cases of OSS-MS. Cases of myelopathy caused by compressive spinal lesions, collagen vascular diseases, and known infectious diseases were carefully excluded. Only the first episode of myelitis in each case was evaluated, and cases in which several recurrent episodes of non-transverse, or partially transverse myelitis finally result in an ATM state were also excluded from ATM-MS.

The percentages of the subtypes of MS were also analyzed according to the year of birth of the patients (1920-1939, 1940-1959, and 1960-1979).

## RESULTS

Fifty-six of the patients were women and 30 were men. The age of onset in these patients was  $29.0 \pm 13$  years and the duration of disease was  $6.0 \pm 6.5$  years. Forty-four patients had C-MS, and 42 had OSS-MS. Twenty patients with MS had ATM, and all of them were the optic-spinal form of MS. ATM was not seen in any case of C-MS. Clinical features and CSF data in the subtypes of MS are summarized in Table 1. The mean onset age (years) of the patients according to the clinical subtypes was 25.5 in C-MS, 34.1 in OSS-MS without ATM, and 30.9 in OSS-MS with ATM. The clinical severity was much greater in OSS-MS with ATM compared with C-MS and OSS-MS without ATM. The CSF findings were not different among these 3 groups.

A great change in the proportions of the clinical subtypes of MS was observed during these thirty years. Among the patients whose onset of the disease was in 1970-1979, 60.0% were cases with OSS-MS with ATM, but such cases significantly decreased to 14.3% in 1980-1989 ( $p < 0.001$  when compared with 1970-1979 by using Fisher's exact test) and only 5% in 1990-1998 ( $p < 0.001$  when compared with 1970-1979) (Fig. 1). The proportion of OSS-MS cases to the total number of MS cases was also significantly decreased to 38.1% in 1980-1989, and 36.8% in 1990-1998 compared with 80.0% in 1970-1979 ( $p < 0.005$  and  $p < 0.01$  respectively). In contrast, the ratios of cases of C-MS to the total number MS cases increased in 1980-1989 (61.9%), and then in 1990-1998 (63.2%) compared with that in 1970-1979 (20.0%) (Fig. 1). The decreases in the proportion of OSS-MS with ATM and OSS-MS without ATM and the increase in C-MS were also confirmed even when the data were analyzed based on the year of birth of the patients (Fig. 2).

TABLE 1. *Clinical features of the two subtypes of multiple sclerosis*

	C-MS ( <i>n</i> = 44)	OSS-MS	
		ATM ( <i>n</i> = 20)	non-ATM ( <i>n</i> = 22)
Female/male (ratio)	25/19 (1.32)	14/6 (2.33)	16/6 (2.67)
Onset age (year)	$25.5 \pm 12$	$30.9 \pm 16$	$34.1 \pm 11$
Duration (year)	$4.9 \pm 5.7$	$8.1 \pm 7.5$	$6.3 \pm 6.9$
EDSS	$3.6 \pm 2.2$	$7.2 \pm 1.5^*$	$3.6 \pm 2.2$
CSF cell count (cells/ $\mu$ l)	$14.1 \pm 3.7$	$16.6 \pm 29$	$28.9 \pm 82$
CSF protein (mg/100 ml)	$44.2 \pm 41$	$45.5 \pm 33$	$52.9 \pm 41$

C-MS, conventional form of multiple sclerosis; ATM-MS, multiple sclerosis with acute transverse myelitis; EDSS, expanded disability status scale; CSF, cerebrospinal fluid; \* $p < 0.01$  when compared with C-MS.

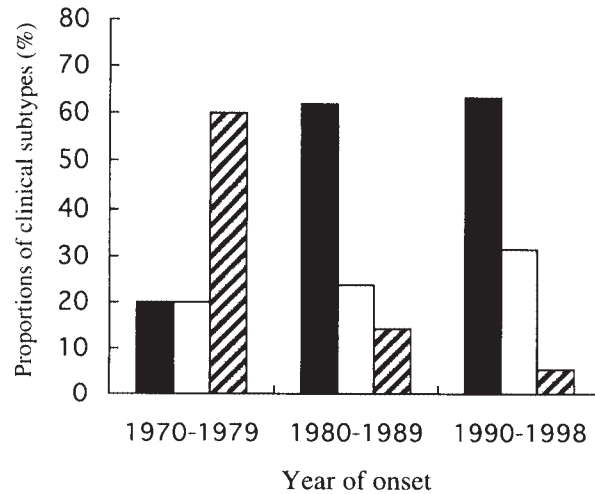


Fig. 1. Proportions of clinical subtypes of multiple sclerosis (MS) in patients whose onsets of MS were in 1970-1979, 1980-1989, and 1990-1998, in Sendai, Japan. All of the patients with ATM had the optic-spinal form of MS, and none of the patients with C-MS had ATM. The percentage of OSS-MS with ATM significantly decreased in 1990-1998 compared to 1970-1979 ( $p < 0.001$ ). In contrast, C-MS increased in 1990-1998 compared to 1970-1979 ( $p < 0.01$ ). C-MS, conventional form of MS; OSS-MS with ATM, optic spinal form of MS with acute transverse myelitis; OSS-MS without ATM, optic-spinal or spinal form of MS without acute transverse myelitis. ■, C-MS; □, OSS-MS (non-ATM); ▨, OSS-MS (ATM).

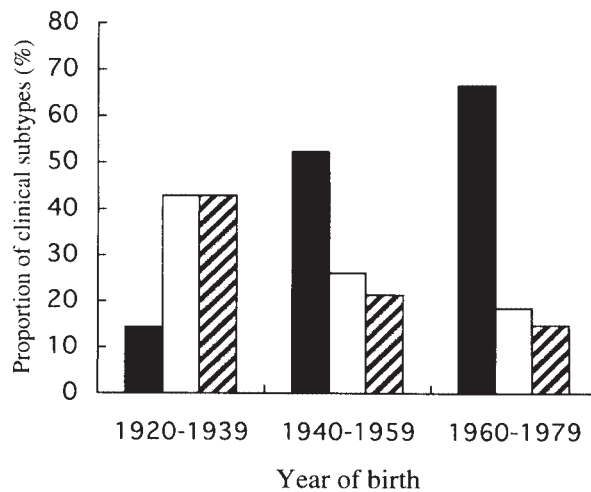


Fig. 2. Proportions of clinical subtypes of multiple sclerosis (MS) in patients who were born in 1920-1939, 1940-1959, and 1960-1979 in Sendai, Japan. All of the patients with ATM had the optic spinal form of MS, and none of the patients with C-MS had ATM. The percentage of OSS-MS with ATM significantly decreased in patients born in 1960-1979 compared to those born in 1920-1939 ( $p < 0.001$ ). C-MS, conventional form of MS; OSS-MS with ATM, optic spinal form of MS with acute transverse myelitis; OSS-MS without ATM, optic-spinal or spinal form of MS without acute transverse myelitis. ■, C-MS; □, OSS-MS (non-ATM); ▨, OSS-MS (ATM).

## DISCUSSION

Our data suggest that the high frequency of the OSS-MS with ATM is an important clinico-epidemiological feature of MS in Japanese patients as compared with Caucasian patients (Shibasaki et al. 1981). However, we have had the impression that cases of typical OSS-MS and MS with ATM have greatly decreased in recent years in Japan. Therefore, the present study was undertaken to verify whether the clinical pictures of MS have changed in the last 30-50 years. As a result, our data suggest that the frequency of cases of MS with ATM as well as OSS-MS markedly decreased during the last 30 years in Sendai, Japan. On the other hand, the frequency of C-MS has increased recently. In other words, the clinical features of Japanese MS have changed and become similar to those of Caucasian MS.

Since the criteria we used in the present study to classify MS subtypes such as C-MS, OSS-MS, and MS with ATM, simple and universal, inter-examiner variation in the results is thought to be insignificant. The diagnostic criteria for ATM are similar to those used by Scott et al. (1998). Moreover, the incidence of ATM-MS in 1970-1979 (60.0%) in our study is comparable to that of the cases of MS with ATM (67%) in the Hawaiians with Oriental ethnicity reported in 1978 (Shibasaki et al. 1978). Thus, we think that our data in Sendai are representative of Oriental MS patients in 1970s.

It is known that patients with non-transverse myelitis often develop MS later (Lipton and Teasdale 1973; Scott et al. 1998), and the majority of these cases are C-MS. On the other hand, ATM is mostly monophasic and does not develop into MS in Caucasian patients (Scott et al. 1998). A study of Japanese MS patients showed that there were a few patients whose initial symptoms of MS were ATM, and about one-fourth of the patients developed ATM during the course of illness (Fukazawa et al. 1990). In that study, most patients with ATM also optic nerve involvement (optic-spinal form of MS), which is similar to our data. Therefore, the pathomechanism of ATM may be distinct from that of non-transverse, or partially transverse myelitis, and the genetic susceptibility to ATM in Japanese and Caucasian MS patients may be different.

Both environmental and genetic factors are involved in the pathogenesis of MS. Linkage analyses of familial MS in Western countries suggested that multiple loci in the human genome, including the HLA locus, are probably associated with susceptibility to MS. Recent HLA genotype analyses in Japanese MS patients demonstrated that DRB1\*1501 and DPB1\*0501 are significantly more common in C-MS and OS-MS, respectively (Ito et al. 1998). This finding suggests that the clinical manifestation of MS may be influenced by HLA and other genetic factors of the patients. In addition to the genetic background, there has been a line of evidence suggesting that environmental factors are related to the pathogenesis of MS. We assume that the genetic background of Japanese remained

largely unchanged for the last 30 years, but nevertheless, the present study showed that the clinical manifestations of MS in Japan have become more similar to those in Western countries. The lifestyle of Japanese people greatly changed to westernized during the last 30 years. Some exogenous factors, such as food, infectious microorganisms, and chemicals in our environment, which may be very similar to those in Western countries, may be responsible for the changes in the clinical manifestations of Japanese MS.

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