

Severe spinal cord involvement is a universal feature of Asians with multiple sclerosis: A joint Asian study

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Abstract

This is a joint clinical study of multiple sclerosis involving 7 regions in Asia. The inclusion criteria were patients who fulfilled the Poser's criteria for clinically definite or laboratory-supported definite multiple sclerosis. A total of 263 patients from Hong Kong, Malaysia, Singapore, Korea, Taiwan, India and Thailand were studied. The mean age of onset was 31 years, and the mean duration of illness was 9.3 years. The clinical course was relapsing remitting in 79% of the patients. The mean relapse rate was 0.86 attacks per annum. Forty percent of the patient had optic-spinal recurrent and 60% had Western forms of multiple sclerosis. The study confirmed features peculiar to the Asian multiple sclerosis noted previously. There was a high female to male ratio of 3.8:1. The female preponderance was more marked among the Chinese, Malays and Thai patients. For the patients from Malaysia and Singapore whose population consisted of Chinese and Malays at a ratio of 1:1.4, there was preponderance among Chinese as compared to Malays with a ratio of 8.6:1. The patients with optic-spinal recurrent and Western forms of multiple sclerosis in this study shared many similarities, including high female to male ratio, mean age of onset, and rate of relapse. When compared to the Western series, both groups of patients had high frequency of acute transverse myelitis, paroxysmal tonic spasm, long segment of spinal cord lesion in MRI, and low rate of positive cerebrospinal fluid oligoclonal band. Severe involvement of spinal cord is thus a universal feature of Asians with multiple sclerosis, seen in both optic-spinal recurrent and Western form of multiple sclerosis.

INTRODUCTION

Studies on multiple sclerosis in Asia has shown significant differences in multiple sclerosis among Asians when compared with the Western counterparts. The differences include lower prevalence, rare occurrence of similar family history, higher incidence of visual failure at the onset of the illness, more severe visual impairment during follow-up, more frequent occurrence of acute transverse myelitis, more severe involvement of spinal cord with greater functional disability, high frequency of paroxysmal tonic spasm, less frequent involvement of cerebellum, more common optic-spinal recurrent form of clinical manifestation, lower incidence of oligoclonal bands in the cerebrospinal fluid, and female preponderance in some of the populations.¹⁻¹⁰ Interestingly, studies from as far as Brazil,^{11,12} Kenya,¹³ Martinique (French West

Indies),¹⁴ and among the black South Africans^{15,16} suggested that these patients have similar clinical features as the Asian patients, whereas those from Libya were more similar to the Western patients.¹⁷

Over the past few years there has been a number of publications on Devic's disease showing its dissimilarities with multiple sclerosis, suggesting that it may be a distinct disease entity.¹⁸⁻²² These publications however used different definitions of Devic's disease. Most of them included patients with optic neuropathy and myelopathy, either as a monophasic disease or part of a multiphasic illness, and the myelopathy may or may not be severe.²³ In Asian literature, Devic's disease has been commonly defined as a monophasic illness with severe bilateral optic neuritis and transverse myelitis occurring successively within several weeks.^{1,2,6,7,9,24} These patients termed Devic's disease in the recent

literature would have been classified as having optic-spinal recurrent form of multiple sclerosis in the Asian literature. As optic-spinal recurrent form of disease is common among Asians, the recent trend to loosen up the definition of Devic's disease raise the question of whether optic-spinal recurrent is a distinct disease entity from multiple sclerosis. It thus has important implication for the Asian neurology practice.

Tan and Chong has shown that severe spinal cord involvement is a universal feature of their with their Malaysian multiple sclerosis patients, occurring in the Western form of multiple sclerosis as well as the optic-spinal recurrent ("Devic's disease") group of patients. This argue against optic-spinal recurrent form of multiple sclerosis as a distinct entity.²³ As the number of Malaysian patients were small, we therefore undertook a cross section survey of multiple sclerosis patients from 7 different regions in Asia to describe and compare the clinical and laboratory features of these patients. In particular, we compare those with optic-spinal recurrent form with the Western form of multiple sclerosis to determine any significant differences in their clinical and laboratory features.

METHODS

We undertook a cross sectional survey of the demography, clinical features, CSF oligoclonal bands and other investigatory findings of multiples sclerosis patients from 22 centres in 7 regions in Asia (Hong Kong, India, Korea, Malaysia, Taiwan, Thailand, and Singapore). Patients with clinical or laboratory-supported definite multiple sclerosis according to the Poser's criteria²⁵ was included. Acute transverse myelitis was defined as an acute illness with onset of less than 4 weeks, with both sensory and motor involvement, the motor involvement being severe and bilateral.²⁶ Optic-spinal recurrent form of multiple sclerosis was defined as patients whose clinical relapses were limited to the optic nerve and spinal cord. Western form of multiple sclerosis was defined as patients whose clinical involvement was beyond the optic nerve and spinal cord. Parametric variables were analyzed with ANOVA while non-parametric nominal variables with Chi square or Fisher's exact test. Non-parametric ordinal variables were analyzed with Mann-Whitney statistics. All p values of less than 0.05 were considered significant.

RESULTS

A total of 290 patients were recruited, 263 patients who satisfied the Poser's criteria for clinical or laboratory-supported definite multiple sclerosis²⁵ were analyzed. The patients were Hong Kong, 79 patients (30%), Malaysia, 58 patients (22%), Singapore, 34 patients (13%), Korea, 31 patients (12%), Taiwan, 27 patients (10%), India, 19 patients (7%), Thailand, 15 patients, (6%). The ethnic composition was: Chinese, 182 patients (69%); Koreans, 31 patients (12%); Indians, 25 patients (10%); Thais, 15 patients (6%), and Malays, 9 patients (3%). In Malaysia and Singapore, both with multi-ethnic population consisting mainly of Chinese and Malays, there were 77 Chinese and 9 Malays with a ratio of 8.6:1. There were 208 (79%) females and 55 (21%) males. The female to male ratio was 3.8:1. The female preponderance was more marked among the Chinese, Malays and the Thais than the Koreans and Indians (Table 1). The mean age of onset was 31 ± 11 year. Only one (0.4%) patient has a family history of multiple sclerosis.

On the clinical course of illness, 207 patients (79%) were relapsing remitting, 19 patients (7%) were secondary progressive, 30 patients (11%) were relapsing progressive, and 7 patients (3%) was primary progressive. The first attack occurred in the spinal cord in 85 patients (33%), in the eyes in 75 patients (29%), and as concurrent optic neuritis and acute transverse myelitis in 10 patients (4%). The brainstem was the first site of attack in 38 patients (14%), cerebrum in 31 patients (12%), cerebellum in 9 patients (4%), and unclear in 8 patients (3%). The mean duration of illness was 9.3 ± 7.9 years, and the mean number of relapses

Table 1: Sex ratio of the multiple sclerosis patients

Ethnic group	Female	Male	Female: male ratio
Caucasian	1	0	1:0
Chinese*	151	31	4.9:1
Indian	17	8	2.1:1
Korean*	16	15	1.1:1
Malay	8	1	8:1
Thai	15	0	15:0
Total	208	55	3.8:1

*Sex ratio significantly different between these two population ($p < 0.001$). The numbers are too small for comparisons to be made with other races.

was 5.2 ± 4.2 . The mean relapse rate was 0.86 ± 0.77 attack per-annum. Ninety-eight (45%) patients had at least a clinical episode of acute transverse myelitis sometimes during the course of their illness. One hundred and twenty seven patients (48%) had at least a clinical episode of optic neuritis. On the other hand, only 64 patients (24%) had an attack in the cerebrum clinically. The onset age of female patients was just as likely to fall outside the reproductive age as their male counterparts (female 17/208 or 8% versus male 5/55 or 9%, $p=0.79$). Paroxysmal tonic spasm was noted in 63 patients (28%), though in 10 patients (16%), there was no other clinical evidence of myelopathy. The Kurtzke's Expanded Disability Scale Score (EDSS) was available in 167 (64%) patients. The median score was 3.8, ranging from 0.0 to 9.0. One hundred and twenty two patients (73%) had scores at or better than 5.5.

Two hundred and two patients had brain magnetic resonance imaging (MRI) and details are available in 179 of them. Out of these 134 patients (66%) showed typical changes of multiple sclerosis. Out of the 128 patients who did not have cerebral involvement clinically, 128 patients had MRI of the brain, and 90 (70%) have changes typical of multiple sclerosis. One hundred and fifty three patients had spinal cord MRI, out of the 137 with details available, 118 (86%) showed changes of myelopathy. Out of the 69 patients who never had myelopathy clinically, spinal cord MRI is available in 26 patients, and 21 patients (81%) showed radiological evidence of spinal cord involvement. Ninety-nine patients (38%) had CSF examination for oligoclonal bands, 27 patients (27%) were positive.

Visual evoked potential was done in 177 patients, 124 (70%) were abnormal. In the 93 patients who had no history of optic neuritis, 50 (54%) were abnormal. Brainstem auditory evoked potential was done in 134 patients, 43 (32%) were abnormal. In the 85 patients without clinical brainstem relapses, 22 (26%) were abnormal. Somatosensory evoked potential was done in 131 patients, 81 (62%) were abnormal. In the 38 patients without myelopathy but has somatosensory evoked potentials tested, 21 (55%) were abnormal.

Treatment detail was available in 207 patients, 93 patients (45%) had β -Interferon. The treatment rate with β -Interferon varied widely from country to country, ranging from 30% to 93% of the patients.

Out of the 220 patients with sufficient details of relapses, 87 patients (40%) had optic-spinal recurrent form of multiple sclerosis. Those with optic-spinal recurrent form of multiple sclerosis were not significantly different from the Western form of multiple sclerosis in the various parameters compared, except higher frequency of acute transverse myelitis and paroxysmal tonic spasm, slightly longer segment of spinal cord involvement in spine MRI and lower frequency of abnormal brain MRI in the optic-spinal recurrent as compared to Western form of multiple sclerosis (Table 2).

DISCUSSION

This joint Asian study with relatively large number of patients from wide geographical distribution confirmed many features peculiar to the Asian multiple sclerosis which has been noted previously, that is: rare occurrence of similar family history, more frequent occurrence of acute transverse myelitis, high frequency of paroxysmal tonic spasm, less frequent involvement of cerebellum, more frequent optic-spinal recurrent form of clinical manifestation, and lower incidence of positive oligoclonal band in the cerebrospinal fluid.¹⁻¹⁰

This study also confirms the high preponderance among females. This is particularly marked among the Chinese, Malays and Thais. However, the Chinese in this study, as in other series that reported high female preponderance, mainly originated from southern coastal provinces of China,^{3,7,10} whereas, the mainland Chinese series from the northern cities of Beijing, Changchun and Harbin have a lower female to male sex ratio of 1.12:1.²⁷ As the age of onset was just as likely to fall outside the reproductive age among females as compared to males, the high female preponderance is probably unrelated to the female sex hormone.

Malaysia and Singapore both consists of multi-ethnic population mainly Malays and Chinese. According to year 2000 census, there were 5.7 Chinese and 11.7 million Malays in Malaysia. According to year 2000 census, the number of Chinese and Malays in Singapore is 3.2 millions and 0.6 millions respectively. The ratio of Chinese to Malay in Malaysia and Singapore is thus 1:1.4. The high prevalence among Chinese versus the Malays of 8.6:1 in this multi-centre study confirms the relative low frequency of multiple sclerosis among Malays as compare to Chinese.^{6,7,9}

Table 2: Comparison between the optic-spinal recurrent and the Western forms of multiple sclerosis

Parameter	Optic-spinal recurrent	Western	P values
Female : Male	3.8:1 (87)	3.0:1 (133)	0.56
Onset age in years	32 ± 12 (87)	30 ± 11 (133)	0.27
Chinese	66% (87)	68% (133)	0.85
Acute transverse myelitis	67% (83)	31% (138)	<0.001
Paroxysmal tonic spasm	46% (87)	16% (125)	<0.001
Abnormal brain MRI	46% (61)	94% (107)	<0.001
Abnormal spinal cord MRI	81% (64)	91% (65)	0.19
No. of lesions in spinal cord MRI	1.2 ± 0.95 (62)	1.5 ± 1.3 (61)	0.37
Length of spinal cord lesion on MRI*	3.8 ± 2.5 (57)	2.9 ± 2.1 (50)	0.016
Abnormal visual evoked potential	70% (60)	70% (108)	0.90
Abnormal median nerve SSEP**	66% (44)	59% (79)	0.61
Cerebrospinal fluid oligoclonal band	14% (37)	33% (55)	0.066
Duration of symptom in years	10 ± 8.4 (87)	8.7 ± 6.6 (133)	0.49
No. of relapses	4.7 ± 3.4 (87)	4.9 ± 2.8 (128)	0.63
Relapse rate per-annum	0.72 ± 0.55 (87)	0.82 ± 0.61 (128)	0.23
Median EDSS [#]	4, range 0-9 (73)	3, range 0-8.5 (88)	0.20

Mean values are shown, with the total number of patients the data based on in parenthesis

*Measured against the height of the adjacent vertebral body.

**median nerve SSEP: median nerve somatosensory evoked potential

[#]EDSS: Kurtzke's Expanded Disability Scale Score

This study shows that the optic-spinal recurrent and Western forms of multiple sclerosis among the Asian patients share many similarities. Both groups of patients have are similar in the high female to male sex ratio, mean age of onset, proportion of Chinese, rate of abnormal visual evoked potential, median nerve somatosensory evoked potential, relapse and disability. It is not unexpected to find the optic-spinal recurrent patients to have higher proportion of acute transverse myelitis, paroxysmal tonic spasm and lower rate of abnormal brain MRI, as the diagnostic criteria of optic-spinal recurrent patients requires that only patients with clinical relapses limited to the spinal cord and optic nerve are included. However, the frequency of acute transverse myelitis and paroxysmal tonic spasm even among the Western form of multiple sclerosis in this series is high when compared to the Caucasian patients. In a comparative clinical study, acute transverse myelopathy was seen in 5% of patients from Britain as compared to 28% of patients from Japan.²⁸ It was 31% of patients with Western form of multiple sclerosis in this study. Paroxysmal tonic spasm was seen in 3.7% and 1.3% of multiple sclerosis patients in two of

the Western series.^{29,30} It was 16% of patients with Western form of multiple sclerosis in this study. Long segment of spinal cord involvement is unusual in the classical multiple sclerosis among the Caucasians.^{18-22,31} The mean length of spinal cord lesion on MRI is longer than two vertebral segments in both the optic-spinal recurrent as well as Western forms of multiple sclerosis in this study. Thus, severe spinal cord involvement is a universal feature of both optic-spinal recurrent and Western forms of Asian multiple sclerosis when compared to Western patients. This finding is similar to Kira et al's study on Japanese patients, where the length of spinal MRI lesion was 5.3 vertebral segments for the Western type of multiple sclerosis, and 6.2 segments for the Asian (optic-spinal) type of multiple sclerosis.³² Both the optic-spinal recurrent and Western forms of multiple sclerosis in this study also have low rate of positive cerebrospinal fluid oligoclonal band, which is also a peculiar feature of Asian multiple sclerosis.^{9,33} These differences in clinical expressions and laboratory findings could be due to genetic make-up, as studies have shown that the optic-spinal recurrent and Western forms of multiple sclerosis have different HLA

associations.^{32,34} Thus, both the optic-spinal recurrent as well as Western forms of Asian multiple sclerosis have significant differences from the classical Western multiple sclerosis, in particular the severe spinal cord involvement. As the recent loosening up of the definition of Devic's disease in the literature implies that the optic-spinal recurrent multiple sclerosis is a distinct disease entity from the Western form of multiple sclerosis among the Asian patients¹⁸⁻²³, this loosening of the term "Devic's disease" should be discouraged.

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