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Long term outcome of multiple sclerosis in Asia

[1]Heng Thay CHONG, [2]Patrick CK LI, [3]Benjamin ONG, [4]Kwang Ho LEE, [5]Ching Piao TSAI, [6]Bhim S SINGHAL, [7]Naraporn PRAYOONWIWAT, [1]Chong Tin Tan

[1]University of Malaya, [2]Queen Elizabeth Hospital, Hong Kong, [3]National University of Singapore, [4]Samsung Medical Center, Seoul, Korea, [5]Veterans General Hospital, Taipei, Taiwan, [6]Siriraj Hospital, Bangkok, Thailand; all members of Multiple Sclerosis in Asia Pacific Study Group

Abstract

This is a cross sectional study to determine the long term outcome of Asians with multiple sclerosis. One hundred and sixty seven patients who fulfilled Poser's criteria for definite multiple sclerosis were assessed for their disability using the Kurtzke's extended disability scale score (EDSS). The mean age was 39.8 $\pm$ 11.4 years, the mean onset age was 30.7 $\pm$ 11.2 years, and the mean duration of illness was 9.1 $\pm$ 7.8 years. The mean EDSS was 3.8, the median 4.0 (range 0 to 9.0). Seventy three patients (44%) had opticospinal multiple sclerosis. On logistic regression analysis, progressive course of disease (OR = 13.4, p = 0.0027), history of transverse myelitis (OR = 6.9, p = 0.0051), incomplete recovery from the first attack (OR = 4.7, p = 0.018) and abnormal somatosensory evoked potentials study (OR = 4.5, p = 0.015) were significantly associated with higher EDSS score. On the other hand, higher number of attack and opticospinal form of disease were not significant factor for increased disability.
In *conclusion*, progressive course of disease and severe spinal relapses were the most important risk factors for long term outcome in Asians with multiple sclerosis.

INTRODUCTION

Multiple sclerosis in Asia and many parts of the world is significantly different from that described in standard text books and seen in the Western countries. Although much is known about the clinical features and radiological features of multiple sclerosis among Asians, little is known about the long term outcomes.[1-8] On the other hand, a number of studies have been undertaken to detail the natural history, the outcome and the prognostic factors that influence the outcomes of multiple sclerosis in Western countries.[9-16] We performed a cross sectional survey involving seven regions in Asia Pacific to document the long term clinical outcome and associated risk factors among multiple sclerosis patients in Asia.

METHODS

The methodology is previously described.[1] Briefly, patients with clinically definite multiple sclerosis according to the Poser's criteria[17] were recruited from 22 centres in 7 regions in Asia (Hong Kong, India, Korea, Malaysia, Taiwan, Thailand and Singapore). 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. Recurrent opticospinal form of multiple sclerosis was defined in patients whose clinical relapses were limited to the optic nerve and spinal cord. The classical ("Western") form of multiple sclerosis was defined as patients whose clinical involvement was beyond the optic nerve and the spinal cord. Parametric variables were analysed with ANOVA while non-parametric variables with χ^2, Fisher's exact test or Mann-Whitney statistics. χ^2 for trend was used to analyze trends of non-parametric variables. For the analysis of prognostic factors, non-parametric variables were separated into groups with EDSS less than 4 or 4 and above for analysis. Multivariate analyses were performed with logistic regression analysis. All p values of less than 0.05 were considered significant.

RESULTS

A total of 167 patients who satisfied Poser's criteria for definite multiple sclerosis, and had assessment of their disabilities using Kurtzke's extended disability scale score (EDSS) were recruited.[18] The mean age was 39.8 $\pm$ 11.4 years, the mean onset age was 30.7 $\pm$ 11.2 years, and the mean duration of illness was 9.1 $\pm$ 7.8 years. The mean EDSS was 3.8, the median 4.0 (range 0 to 9.0). Seventy three patients (44%) had opticospinal multiple sclerosis and cerebrospinal fluid oligoclonal bands were positive in 18 patients (out of 81, 22%). The other characteristics are

detailed in Table 1. The progression of disability as a function of duration of illness is detailed in Table 2.

Table 3 detailed the parameters that were statistically significantly related to higher EDSS scores. In particular, patients with progressive disease, older onset age and older age when assessed, longer duration of illness, history of transverse myelitis or paroxysmal tonic spasm, incomplete recovery from the first attack, and abnormal somatosensory evoked potential study were found to have higher EDSS scores. Patients with opticospinal form of multiple sclerosis did not have higher level of disabilities compared with those with classical disease, and neither did the patients with first attack of cerebellar disease had lower EDSS scores than the others. The total number of attack was also not a significant factor. On logistic regression analysis, only the following are found to be significant – progressive disease (OR = 13.4, p = 0.0027), history of transverse myelitis (OR = 6.9, p = 0.0051), incomplete recovery from the first attack (OR = 4.7, p = 0.018) and abnormal somatosensory evoked potentials study (OR = 4.5, p = 0.015).

Table 1: Recruitment and demography (n=167)

Parameter		No. (%)
Region	Malaysia	39 (23)
	Hong Kong	37 (22)
	Korea	30 (18)
	Taiwan	27 (16)
	India	19 (11)
	Thailand	15 (9)
Ethnicity	Chinese	32 (55)
	Korean	30 (18)
	Indian	24 (14)
	Thais	15 (9)
	Malay	6 (4)
Sex	Female	127 (76)
	Male	40 (24)
Course	Relapsing-remitting	125 (75)
	Secondary progressive	10 (6)
	Relapsing progressive	30 (18)
	Primary progressive	2 (1.2)

DISCUSSION

Severe spinal relapses are more common in patients with multiple sclerosis in Asia[1], and previous reports have suggested that patients in Asia had more severe disabilities compared with patients in western countries.[5,8,19] Our current study is consistent with these findings. A 50-year prospective population study in Iceland showed that after 25 years or more, 52% of the subjects still had an EDSS of 3.5 or less, while a population study in Australia showed that 56.9% of the subjects reached EDSS of 4 or above only after 10 - 14 years of illness.[12] Another study showed

Table 2: Disease duration and disability

	EDSS (%)			
Duration (years)	**0 to 3.5**	**4 to 6.5**	**7 to 9.5**	**Total**
0 to 4	33 (56%)	24 (40%)	2 (4%)	59
5 to 9	27 (52%)	17 (33%)	8 (15%)	52
10 to 14	9 (35%)	12 (46%)	5 (19%)	26
15 to 19	5 (39%)	2 (15%)	13 (46%)	13
20 to 24	5 (50%)	2 (20%)	10 (30%)	10
25 to 29	0 (0%)	1 (50%)	2 (50%)	2
30 to 34	0 (0%)	0 (0%)	1 (100%)	1
35 to 39	1 (33%)	0 (0%)	2 (67%)	3
40 to 44	1 (100%)	0 (0%)	0 (0%)	1
Total	81 (48%)	58 (35%)	28 (17%)	167

Table 3: Prognostic factors and EDSS

Parameters		No.	Median EDSS	p value
Sex (median)	Female	127	3.0	0.44
	Male	40	4.3	
Form of multiple sclerosis	Opticospinal	72	4.0	0.44
	Classical	95	3.0	
Course	Progressive	42	5.8	<0.001
	RRMS	125	2.5	
Onset age	0 – 9	1	1.0	0.16
	10 – 19	29	3.0	
	20 – 29	52	3.5	
	30 – 39	51	4.0	
	40 – 49	23	4.0	
	50 – 59	9	5.0	
	60 – 69	2	4.8	
Age	10 – 19	18	2.3	0.022
	20 – 29	23	3.0	
	30 – 39	55	3.0	
	40 – 49	48	4.8	
	50 – 59	27	4.0	
	60 – 69	7	5.5	
	70 – 79	1	7.5	
Duration (years)*	0 – 9	114	3.0	0.036
	10 – 19	35	4.5	
	20 – 29	13	5.0	
	30 – 39	4	7.3	
	40 – 49	2.0	1	
History of transverse myelitis	Yes	83	5.0	0.00055
	No	79	2.5	
Complete recovery	Yes	104	3.0	0.010
from first attack	No	57	5.0	
History of paroxysmal	Yes	49	5.0	0.036
tonic spasm	No	115	3.0	
First attack – spinal	Yes	56	4.5	0.17
	No	106	3.5	
Number of attacks*	0 – 4	106	3.0	0.088
	5 – 9	52	4.0	
	10 – 14	7	7.0	
	15 – 19	1	6.5	
	20 – 24	1	2.5	
Number of spinal attacks*	0 – 4	147	3.0	0.061
	5 – 9	17	6.0	
	10 – 14	1	7.5	
	15 – 19	2	4.5	
Somatosensory	Abnormal	58	5.0	0.0028
evoked potentials	Normal	36	2.3	

* Outliers excluded from analysis.

that after 12 years of illness, only about 37 - 52% of patients reached an EDSS of 5 or higher.[10] In our study, about half of the patients reached an EDSS of 4 by about 5 to 9 years of illness (5 to 10 years earlier than patients in the West) and 15% of these patients reached an EDSS of 7 and above, consistent with an earlier study that found 17% of patients were bedridden after an average of 5 years of illness.[8] This is also consistent with a study that showed that African-Americans, who have similar clinical disease as Asians, had more significant disabilities compared with Caucasian Americans.[4] Another study in the region had shown that after as little as 7.1 years of the illness, 47.3% of the patients were severely disabled or bed-ridden, and mortality was as high as 28.9%.[19] Even then, our study probably underestimated the severity of the disease in view of the previous reports of high mortality among Asian with multiple sclerosis[5,19], and the fatal cases who are often severely disabled prior to death are not included in this study. Furthermore, patients with more severe disabilities are less likely to seek medical attention, partly due to poorer transportation system in many parts of the region, and the perception that the health care system had little to offer to them.

Contrary to other studies[12,20], the lack of statistically significant association between more severe disabilities with sex, age and onset age may reflect the small sample size of our study.

The most important risk factor for long term disability in this study of Asians with multiple sclerosis is similar to others – that of progressive course of disease.[9-13] However, for our Asian patients, the next most important prognostic factor is involvement of the spinal cord. This is especially so when there is severe disease, expressed clinically as transverse myelitis and as persistent abnormalities seen in somatosensory evoked potential study. This supports the notion that spinal cord relapses are more important than relapses elsewhere in the long term outcome of multiple sclerosis among Asians. On the other hand, patients with opticospinal disease have similar degree of disabilities as patients with classical disease. Since the outcome of the disease reflects the underlying disease activities and progression[9,21], this suggests that regardless of the spectrum of clinical manifestation, the underlying disease progressions are similar in these two groups of patients.

The finding of severe spinal relapses affect long term outcome has important implications in the management of the disease. Firstly, somatosensory evoked potential study, though less sensitive to imaging studies of the spinal cord, nonetheless provides important prognostic significance. Secondly, patients with severe spinal cord relapses without complete recovery are at risk of more severe morbidity. In future studies on multiple sclerosis among Asians, priorities should be given to addressing the management option of the patients who manifest severe spinal cord relapses despite being given established disease modifying agents such as beta interferon.

REFERENCES

1. Chong HT, Li PCK, Ong B, Lee KH, Tsai CP, Singhal BS, Prayoonwiwat N and Tan CT. Severe spinal cord involvement is a universal feature of Asians with multiple sclerosis: a joint Asian Study. *Neurol J Southeast Asia* 2002; 7: 35 – 40
2. Chong HT, Ramli N, Lee KH, Kim BJ, Ursekar M, Dayananda K, Singhal BS, Chong J, Chan LL, Seetoh YY, Chawalparit O, Prayoonwiwat N, Chang CP, Tsai CP, Tang KW, Li PCK, Tan CT. Magnetic resonance imaging of Asians with multiple sclerosis was similar to that of the West. *Neurol J Southeast Asia* 2004; 9: 47 – 53.
3. Thirugnanam U. Multiple sclerosis: a retrospective review of 30 cases from Singapore. *Neurol J Southeast Asia* 1997; 2: 171 – 5.
4. Cree BAC, Khan O, Bourdette D, Goodin DS, Cohen JA, Marrie RA, Glidden D, Weinstock-Guttman B, Reich D, Patterson N, Haines JL, Pericak-Vance M, DeLoa C, Oksenberg JR and Hauser SL. Clinical characteristics of African Americans versus Caucasian Americans with multiple sclerosis. *Neurology* 2004; 63: 2039 – 45.
5. Tan CT. Multiple sclerosis in Malaysia. *Arch Neurol* 1988; 45(6): 624 – 7.
6. Vejjajiva A. Multiple sclerosis in Thailand. *Neurol J Southeast Asia* 1997; 2: 7 – 10.
7. Kuroiwa Y, Igata A, Itahara K, Koshijima S, Tsubaki T. Nationwide survey of multiple sclerosis in Japan. Clinical analysis of 1, 084 cases. *Neurology* 1975; 25: 845 – 851.
8. Kuroiwas Y, Hung TP, Landsborough D, Park CS and Singhal BS, Soemargo S, Vejjajiva A and Shibasaki H. Multiple sclerosis in Asia. *Neurology* 1977; 27: 188 – 92.
9. Confavreux C, Vukusic S, Moreau T and Adeleine P. Relapses and progression of disability in multiple sclerosis. *N Eng J Med* 2000; 343: 1430 – 8.
10. Bergamaschi R, Montomoli C, Candeloro E, Fratti C, Citterio A and Cosi V. Disability and mortality in a cohort of multiple sclerosis patients: A reappraisal. *Neuroepidemiology* 2005; 25: 15 – 8.
11. Amato MP and Ponziani G. A prospective study on the prognosis of multiple sclerosis. *Neurol Sci* 2000; 21: S831 – 8.
12. Hammond SR, McLeod JG, Macaskill P and English DR. Multiple sclerosis in Australia: prognostic factors. *Journal of Clinical Neuroscience* 2000; 7(1): 16 – 9.

13. Benedikz J, Stefansson M, Guomundsson J, Jonasdottir A, Fossdal R, Gulcher J and Stefansson K. The natural history of untreated multiple sclerosis in Iceland. A total population-based 50 year prospective study. *Clinical Neurology and Neurosurgery* 2002; 104: 208 – 10.
14. Hawkins SA and McDonnell GV. Benign multiple sclerosis? Clinical course, long term follow up, and assessment of prognostic factors. *J Neurol Neurosurg Psychiatry* 1996; 67: 148 – 52.
15. Simone IL, Carrara D, Tortorella C, Liguori M, Lepore V, Pellegrini F, Bellacosa A, Ceccarelli A, Pavone I and Livrea P. Course and prognosis in early-onset multiple sclerosis. *Neurology* 2002; 59: 1922 – 8.
16. Martinelli V, Rodegher M, Moiola L and Comi G. Late onset multiple sclerosis: clinical characteristics, prognostic factors and differential diagnoses. *Neurol Sci* 2004; 25: S350 – 5.
17. Poser CM, Paty DW, Schonberg L, McDonald I, Davies FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol*, 1983; 13: 227 – 31.
18. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33(11): 1444-52.
19. Tan CT. Multiple sclerosis and other related diseases in Malaysia: Their clinical manifestations and laboratory findings. Doctor of Medicine thesis, University of Malaya, 1990.
20. Hawkins SA and McDonnell. Benign multiple sclerosis? Clinical course, long term follow up, and assessment of prognostic factors. *JNNP* 1999; 67: 148 – 152.
21. Ebers GC. Natural history of multiple sclerosis. *JNNP*, 2006; 71(SII): ii16 – ii19.