

Associations of MRI-lesions and clinical features with disability in Chinese patients with multiple sclerosis

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Abstract

Objective: To analyze associations of MRI-lesions and clinical features with disability in patients with multiple sclerosis (MS) in Shanghai, China. **Methods:** We studied patients with MS, identified from a survey in Shanghai, whose sites of lesions in the CNS was based on the MRI examinations. Associations between MRI-lesions, various clinical variables and the severity of disability were analyzed with univariate and multivariate logistic regression analysis. **Results:** There were 210 patients in this study. The disability of the patients with lesions confined to the spinal cord was significantly more severe than those with lesions in the brain ($p < 0.008$). Current age (OR: 1.041, 95% CI: 1.007~1.077), MS duration (OR: 1.082, 95% CI: 1.011~1.159) and MRI-lesions in the spinal cord (OR: 2.441, 95% CI: 1.039~5.737) were significantly associated with severity of disability on multivariate logistic regression analysis.

Conclusion: MRI-lesions in the spinal cord, older age, a longer MS duration were significantly associated with a more severe disability in this MS study in Shanghai China.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, relapsing disorder and characterized by multiple lesions in time and space in the central nervous system (CNS). It is thought to be one of the most important CNS diseases affecting activities of daily living.^{1,2} Early intervention with long-term treatments is important to achieve a better prognosis. There is thus an urgent need to understand better which clinical features would be associated with, and predictive of the long term disability.

There have been several reports from the western countries describing the possible associations with disability in patients with MS. Several clinical variables, such as the age at onset, current age, gender, disease course, and the sites of demyelinating lesions in the

CNS, were thought to be important.³⁻⁹ A study from the USA found that duration and clinical course of illness were the major predictors of disability.¹⁰ However, a number of studies have shown that the clinical features of MS vary in different geographic areas¹¹⁻¹⁴, indicating that the predictors of disability may also be different in different populations. Among the Chinese, MS is characterized by more frequent optic nerve and spinal cord involvement.^{15,16} The purpose of this study was to determine the associations between clinical features, MRI-lesions and the disability among Chinese patients with MS, based on a large survey in Shanghai, China.^{15,16}

METHODS

A large epidemiological survey was conducted

from September 1, 2004 to August 31, 2005 to identify and investigate all prevalent patients with MS in 11 districts in Shanghai.^{15,16} A network of physicians, mainly neurologists, from 55 hospitals was established to actively identify and report prevalent MS patients. The inpatient register of each hospital in the study area was also systematically checked for the diagnosis of MS, neuromyelitis optica (NMO), or other demyelinating disorders. Senior neurologists took part in each step of the investigation, including case finding, completion of study protocols, and validation of diagnosis. Two hundred and forty nine patients were identified and diagnosed with MS according to the McDonald criteria.¹⁷ Information was collected from each of these patients, including the demographic details, past medical history, initial symptom(s), age of onset, clinical manifestations, and results of MRI scans. Patients with only myelitis, or optic neuritis, or neuromyelitis optica (NMO) were excluded from the study.

Patients in whom the sites of MS lesions in the CNS could be clearly determined based on the MRI examinations were included in the analysis. All MRI examinations were taken during hospitalization at the disease onset or relapse. According to the sites of MS lesions on MRI (MRI-lesions), patients were classified into the following groups: with lesions in the brain, with lesions in the spinal cord, and with lesions in both the brain and the spinal cord. According to the neurological functional status, the activities of daily living (ADL) were defined in four levels: 1, not affected and no disability; 2, mild disability, capable of most self-care, need for help in bathing; 3, severe disability, need help for many activities; and 4, complete disability, wheelchair bound or bedridden.¹⁸

Ethics approval was obtained from the Ethics Committee of the Ruijin Hospital, Medical School of the Shanghai Jiao Tong University.

Statistics analysis

Statistical analyses were accomplished by using the SPSS (Statistical package for the Social Sciences) for Windows. Student's t-test or ANOVA was conducted for continuous data and comparison of the mean between groups. Differences between proportions were assessed using chi-square test or Fisher's exact test when appropriate. For nonparametric data, Mann-Whitney test or Kruskal-Wallis H test was used.

Univariate and multivariate logistic regression

analyses were performed to identify associations between MRI-lesions, clinical features and the severity of disability, which was the dependent variable and coded as: 0, without or mild disability; 1, severe or complete disability. Odds ratios were calculated with 95% confidence intervals (CI). Various clinical variables were examined first in the univariate logistic regression analysis, like gender, current age, age at onset, number of attacks, MS duration, initial symptom/s, and MRI-lesions. Variables with statistical significance in the univariate analysis were entered in the model by means of a forward stepwise logistic regression procedure until all variables in the model made a significant contribution ($p < 0.05$). Variables of age at onset, current age, and MS duration were grouped as categorical variables in the univariate logistic regression analysis, and entered with original values as continuous variables in the multivariate logistic regression analysis.

RESULTS

There were 210 (88 male and 122 female) patients, whose sites of MS lesions in the CNS were determined according to the MRI examinations, were included in this analysis. The mean current age at the prevalence day (December 31, 2004) was 43.1 (SD 14.0) years; 43.4 (SD 13.6) years for males and 42.9 (SD 14.5) years for females.

Clinical features of patients by MRI-lesions are listed in Table 1. The number of patients in each group of "Brain", "Spinal cord" and "Brain & spinal cord" was 120, 49, and 41, respectively. For the patients with MRI lesions confined to the spinal cord, all had optic neuritis (bilateral or unilateral), thus fulfilling the diagnostic criteria of MS. Differences between the three groups were not statistically significant for the following variables: current age ($p=0.114$), age at onset ($p=0.109$), MS duration ($p=0.537$) and number of attacks ($p=0.078$). Distribution of the patients according to the site of MS lesions in the CNS is presented in Figure 1.

The levels of disability according to the MRI-lesions are listed in Table 2. More than 60% of the patients with MRI-lesions in the brain were without disability. Compared to the patients with MRI-lesions in the brain, the proportion with poorer activities of daily living was significantly high ($p=0.008$) among patients with MRI-lesions in the spinal cord.

The levels of disability according to a number of variables in the groups of different MRI-lesions are listed in Table 3. A significantly longer MS

Table 1: Features of patients with MS by group of different MRI lesions

Features	MRI-lesions in the CNS, Mean ± SD			
	Brain (n=120)	Spinal cord (n=49)	Brain & spinal cord (n=41)	Total (n=210)
Current age, years	42.2 ± 14.6	46.7 ± 12.6	41.5 ± 13.7	43.1 ± 14.1
Age at onset, years	36.6 ± 14.6	41.5 ± 12.0	37.0 ± 14.3	37.8 ± 14.1
MS duration, years	5.6 ± 5.2	5.2 ± 5.8	4.5 ± 3.8	5.3 ± 5.1
Number of attacks	2.4 ± 0.7	2.6 ± 0.5	2.6 ± 0.5	2.5 ± 0.6

duration was observed for the patients with severe disability in the group of “Brain” (p=0.024). In the group of “Spinal cord”, the current age was significantly higher for patients with severe or complete disability than the other patients in the group (p=0.039).

Patients with MRI-lesions in the brain

The 120 patients with MS lesions in the brain were further divided into: “Supratentorial”, “Infratentorial” and “Supratentorial & Infratentorial”. The number of patients in each group was 67, 17, and 37, respectively (Table 4). In the “Supratentorial” group, the MS duration was longer for the patients with severe disability than the other patients in the section. In the “Infratentorial” group, where there were patients only in two levels of disability (mild or without

disability), the MS duration for the patients with mild disability was longer than the patients without disability. However, no statistically significant differences were observed.

Patients with MRI-lesions in the spinal cord

The 49 patients with MRI-lesions in the spinal cord were classified in three groups: “Cervical cord”, “Thoracic cord”, “Cervical & thoracic cord”, and the number of patients in each group was 19, 15, and 11, respectively. The other 4 patients: one patient with the lesion in the lumbar cord, another one with the lesion in both the thoracic and lumbar cord, and the other two patients with diffuse lesions in the spinal cord were not included in the analysis. The most frequent MRI-lesions in the spinal cord were located in the cervical cord, followed by the thoracic cord.

Figure 1. Distribution of patients according to the site of MS lesions in the CNS (n=210).

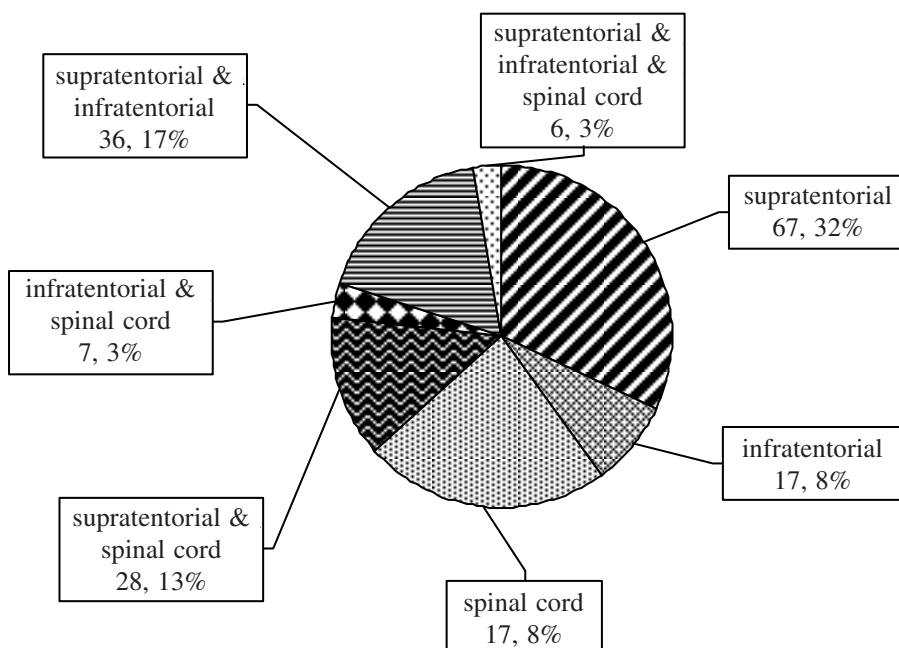


Table 2: The activities of daily living according to the MRI-lesions in the MS patients

Activities of daily living [≠]	Brain*		Spinal cord*		Brain & Spinal cord		Total	
	Cases	Percent	Cases	Percent	Cases	Percent	Cases	Percent
Not affected and no disability	81	67.5	24	49.0	26	63.4	131	62.4
Mild disability, capable of most self-care, need help in bathing	28	23.3	13	26.5	10	24.4	51	24.3
Severe disability, need help for many activities	9	7.5	11	22.4	3	7.3	23	10.9
Complete disability, wheelchair bound or bedridden	2	1.7	1	2.1	2	4.9	5	2.4
Total	120	100.0	49	100.0	41	100.0	210	100.0

*p=0.008 between the groups of “Brain” and “Spinal cord”.

Table 3: The levels of disability according to a number of variables in the groups of different MRI-lesions in the MS patients (n=210)

Activities of daily living*	Brain				Spinal cord				Brain & spinal cord						
	No.	Current age, yrs	Age at onset, yrs	MS duration, yrs	No. attacks	Number of attacks	MS duration, yrs	Age at onset, yrs	Current age, yrs	No. attacks	Number of attacks	MS duration, yrs	Age at onset, yrs	Current age, yrs	No. attacks
1	81	41.6±14.4	36.8±14.4	4.8±3.9	2.4±0.7	24	43.7±12.9	39.6±12.7	4.1±4.0	2.6±0.6	26	40.2±13.7	36.5±14.4	3.7±3.4	2.5±0.5
2	28	43.3±14.5	37.1±14.1	6.2±4.9	2.4±0.6	13	44.1±8.6	38.7±9.3	5.4±5.4	2.6±0.5	10	40.3±13.9	33.5±15.5	6.8±4.4	2.7±0.5
3	9	45.0±18.6	35.0±19.7	10.0±11.5	2.8±0.4	11	55.5±12.8	47.9±11.7	7.5±8.8	2.7±0.5	3	46.4±10.8	43.6±9.3	2.8±1.9	2.3±0.6
4	2	37.7±5.1	30.0±4.0	7.7±1.2	2.5±0.7	1	58.3	53.7	4.6	3.0	2	57.8±11.8	50.4±10.7	7.4±1.1	3.0±0.0
p value (column)		0.841	0.908	0.024	0.418		0.039	0.137	0.446	0.797		0.323	0.405	0.078	0.359

*Activities of daily living: 1. Not affected and no disability; 2. Mild disability, capable of most self-care, need help in bathing; 3. Severe disability, need help for many activities; 4. Complete disability, wheelchair bound or bedridden.

Table 4: The levels of disability according to a number of variables and sites of lesion in the MS patients with MRI-lesions in the brain (n=120)

Activities of daily living*	Supratentorial				Infratentorial				Supratentorial & Infratentorial						
	No.	Current age	Age at onset	MS duration	Number of attacks	No.	Current age	Age at onset	MS duration	Number of attacks	No.	Current age	Age at onset	MS duration	Number of attacks
1	43	39.9±14.4	34.5±15.0	5.4±4.4	2.4±0.8	14	42.7±14.1	39.3±12.6	3.4±2.6	2.2±0.7	24	43.9±14.8	39.4±14.3	4.5±3.4	2.5±0.7
2	15	42.6±14.4	36.4±14.2	6.2±5.4	2.5±0.6	3	48.8±20.8	42.6±17.3	6.3±5.3	1.7±0.6	10	42.7±14.2	36.5±14.4	6.2±4.4	2.5±0.5
3	8	46.1±19.6	35.0±21.0	11.2±11.7	2.8±0.5	0	-	-	-	-	1	36.2	35.7	0.6	3.0
4	1	41.3	32.8	8.5	3.0	0	-	-	-	-	1	34.0	27.2	6.8	2.0
p value (column)		0.728	0.980	0.097	0.464		0.534	0.704	0.168	0.228		0.877	0.818	0.381	0.769

*Activities of daily living: 1. Not affected and no disability; 2. Self-care basically, need for help in bathing; 3. Severe disability, need help for many activities; 4. Complete disability, wheelchair/bedridden.

Although the MS duration was longer for patients with severe disability in the “Cervical cord” and “Thoracic cord” groups, the differences were not statistically significant, perhaps because of the small numbers of patients in each category. The current age was significantly higher ($p = 0.023$) among patients with severe disability (56.6 ± 9.8 years) than those with mild (39.4 ± 5.1 years) or without disability (40.1 ± 12.1 years) in the “Thoracic cord” group.

Associations of clinical features and MRI-lesions with disability

Results from the univariate logistic regression analysis are presented in Table 5. The current age of 60 years or older (OR: 17.500, 95% CI: 1.967~155.592), MS duration of 192 months (16 years) or longer (OR: 9.500, 95% CI: 2.354~38.332), number of attacks of 3 times or more (OR: 2.446, 95% CI: 1.025~5.837), MRI-lesions in the spinal cord (OR: 2.308, 95% CI: 1.022~5.210) as well as spinal cord symptom(s) as initial symptom(s) (OR: 2.250, 95% CI, 1.006~5.032) were significantly associated with severe or complete disability. However, only the current age (OR: 1.041, 95% CI: 1.007~1.077), MS duration (OR: 1.082, 95% CI: 1.011~1.159) and MRI-lesions in the spinal cord (OR: 2.441, 95% CI: 1.039~5.737) were significant in multivariate logistic regression analysis for the association with disability in patients with MS (Table 6).

DISCUSSION

MRI can be helpful to identify MS lesions in the brain and the spinal cord and there have been previous reports of associations between MS lesions on MRI and clinical disability.^{14,19-22} This study aimed to investigate associations between MRI-lesions, clinical features and the severity of disability in MS patients in Shanghai, China. Our patients were from the largest case-series of Chinese patients with MS identified from a survey.^{15,16} All patients in the current analysis were examined by MRI scans which determined the sites of MS lesions. Therefore, the validity of the MS diagnosis and the sites of MS lesions are good. Only 39 patients (15.7%) from the original case series were excluded because they did not have MRI scans or the sites of MS lesions in the CNS could not be clearly determined. Our findings indicated a disparity between the disability and the site of MRI-lesions in the CNS.

Table 5: Results of univariate logistic regression analysis for associations between clinical variables and disability in patients with MS

Clinical variables	Code*	No. of patients	No. of patients with severe or complete disability (%)	OR (95% CI)
Gender				
Male	0	88	13 (14.8)	1
Female	1	122	15 (12.3)	0.809 (0.364-1.799)
Current age, years				
< 30	0	36	1 (2.8)	1
30-59	1	153	20 (13.1)	5.263 (0.683-40.582)
≥60	2	21	7 (33.3)	17.500 (1.968-155.592)
Age at onset, years				
< 20	0	27	2 (7.4)	1
20-39	1	86	10 (11.6)	2.138 (0.451-10.132)
40-59	2	89	13 (14.6)	1.645 (0.337-8.017)
≥60	3	8	3 (37.5)	7.500 (0.984-57.138)
MS duration, months				
<96	0	172	20 (11.6)	1
96-191	1	29	3 (10.3)	0.877 (0.243-3.163)
≥192	2	9	5 (55.6)	9.500 (2.354-38.332)
Number of attacks				
≤2	0	98	8 (8.2)	1
≥3	1	112	20 (17.9)	2.446 (1.025-5.837)
Site of lesions				
Spinal cord				
No	0	120	11 (9.2)	1
Yes	1	90	17 (18.9)	2.308(1.022-5.210)
Initial symptom/s				
Visual impairment				
No	0	175	23 (13.1)	1
Yes	1	35	5 (14.3)	1.101 (0.388-3.127)
Spinal cord				
No	0	140	14 (10.0)	1
Yes	1	70	14 (20.0)	2.250 (1.006-5.032)

* Codes used in the univariate logistic regression analyses

Table 6: Results of multivariable logistic regression analysis for associations between clinical variables and disability in patients with MS

Clinical variables	OR	95% CI	p Value
Current age	1.041	1.007-1.077	0.019
MS duration	1.082	1.011-1.159	0.023
Spinal cord lesions	2.441	1.039-5.737	0.041

The disability of the patients with MRI-lesions in the spinal cord was worse than that in the patients with MRI-lesions in the brain, which is consistent with previous reports.^{7,23-25} We also found from univariate logistic regression analysis that patients with spinal cord symptom(s) as their initial symptom(s) and MRI-lesions in the spinal cord had worse disability. This is consistent with the previous study showing that it took longer to reach irreversible disability in patients without long tract involvement as initial symptoms.⁶ These findings suggest that the lesions in the spinal cord could be more relevant to activities of daily living in patients with MS. The activities of daily living is closely related with motor movement, which is largely determined by the pyramidal tract in the CNS, and vulnerable to lesions in the spinal cord. On the other hand, MS lesions in the brain, especially the subcortical lesions, are often located in the neurologically “silent” areas. These small and disseminated demyelinating lesions may only result in little or subtle neurologic deficit.

As we described previously, the proportion of patients with the so-called opticospinal MS (OS-MS) in our series was more than 20%.¹⁶ MS with main lesions confined to the optic nerve and spinal cord, with no evidence of lesions in the cerebrum or cerebellum as well as with a few brainstem signs during the course, is classified as OS-MS, while patients with lesions at multiple sites in the CNS, including the cerebrum, cerebellum or brainstem, are classified as having conventional (C-MS).¹⁴ In our experience, it is difficult to distinguish MS and NMO at the early stage of the disease. With the disease progression, some patients with a diagnosis of NMO could later be diagnosed as MS. Evidence exists to support that NMO is pathologically distinct from MS²⁶, but the relationship between the two remains to be further clarified, despite the discovery of anti-AQP4 antibody.²⁷

We have found that for the patients with MS lesions in the brain, the MS duration was significantly longer in patients with more severe disability. (Table 3) This suggests a deterioration of the MS lesions in the CNS from disease progression.

It is not possible for us to make further analysis on the impact of disease progression because we do not have long-term follow-up data, which is the main limitation of this study. Scalfari *et al.*²⁸ reported the relationship between relapse and long-term disability in MS, based on 806 patients with 28,000 patient-years of evolution. Their conclusion was “Preventing, delaying or

attenuating the progressive phase of the disease are the key therapeutic targets in MS”, while the relapses (except possibly during the first 2 years) may not be a valid outcome surrogate for the late disability.

The current age was found to be significantly associated with more severe disability in this study. This is consistent with several previous studies, which indicated that distinct and heterogeneous pathogenesis pathways might operate at different periods in individual patients.²⁹ At a younger age, disability might be attributed principally to inflammatory processes³⁰, and at an older age, from progressive axonal loss.³¹⁻³⁵ However, the association was not statistically significant between the age at onset and disability in our study. Results from several previous studies indicated an early age of disease onset was a positive prognostic factor for disability in MS.³⁶⁻³⁸

Mowry *et al* reported that the onset location was able to predict the location of subsequent relapses.³⁹ We could not analyze the predictive role of onset location on the long term disability in this study. Although this study was based on an epidemiological survey in Shanghai, some of the information was obtained from hospital records. However, the duration of disease of some our patients was long, which made it difficult for the patients to recall their first symptoms clearly.

A limitation of this study is that it is a retrospective study, and some patients had only a brain or spinal cord MRI. The details of the MRI examinations, such as the MRI sequences, MRI scanners, and slice thickness were also not uniform. Furthermore, the neurological functional status was defined according to the ADL, which might not be as good as EDSS or other MS-specific assessment tools. Therefore, further prospective studies are needed to confirm our finding.

In conclusion, older age, a longer MS duration, and MRI-lesions in the spinal cord were significantly associated with a more severe disability in this study based on MS patients in Shanghai, China.

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DISCLOSURE

Conflict of interest: None.

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