

# Magnetic Resonance Imaging of Asians with Multiple Sclerosis was Similar to that of the West

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**ABSTRACT:** Magnetic resonance imaging (MRI) of the brain is the most important paraclinical diagnostic test in multiple sclerosis (MS). The appearance of MRI in Asians with MS is not well defined. We retrospectively surveyed the first brain and spinal cord MRI in patients diagnosed to have MS, according to Poser's criteria in seven regions throughout Asia to define the MRI changes among Asians with MS. There were 101 patients with first brain, and 86 with first spinal cord MRI, 66 of whom had both. The brain MRI showed a mean of 17 lesions per patient in T2 weighted images, mostly asymptomatic. Almost all the lesions were in the white matter, particularly in the juxtacortical, deep and periventricular white matter. A third of the lesions were greater than 5 mm, 14% enhanced with gadolinium. There were more supratentorial than infratentorial lesions at a ratio of 7.5: 1. Ninety five percent of the spinal cord lesions were in cervical and thoracic regions, 34% enhanced with gadolinium. The lesions extended over a mean of  $3.6 \pm 3.3$  vertebral bodies in length. Fifty (50%) of the brain and 54 (63%) of the spinal MRI patients had the optic-spinal form of MS. The MRI of the optic-spinal and classical groups of patients were similar in appearance and distribution, except that the optic-spinal MS patients have fewer brain but longer and more severe spinal cord lesions. In conclusion, the brain and spinal cord MRI of Asian patients with MS was similar to that of the West, although, in this study, Asian MS patients had larger spinal cord lesions.

**RÉSUMÉ:** L'imagerie par résonance magnétique est similaire chez des patients atteints de sclérose en plaques, qu'ils soient d'Asie ou de l'Ouest. L'imagerie par résonance magnétique (IRM) du cerveau est l'épreuve diagnostique paraclinique la plus importante dans la sclérose en plaques (SEP). Les caractéristiques de l'IRM chez les Asiatiques atteints de SEP sont mal connues. Nous avons analysé rétrospectivement l'IRM initiale du cerveau et de la moelle épinière chez des patients dont le diagnostic de SEP avait été fait selon les critères de Poser dans sept régions d'Asie, afin de préciser les changements observés à l'IRM chez des Asiatiques atteints de SEP. L'imagerie du cerveau était disponible chez 101 patients, celle de la moelle épinière chez 86 patients et celle du cerveau et de la moelle épinière chez 66 patients. À l'IRM du cerveau, le nombre moyen de lésions par patient était de 17 sur les images pondérées en T2, ces lésions étant en grande partie asymptomatiques. Presque toutes les lésions étaient situées dans la substance blanche, surtout juxtacorticale, profonde et périventriculaire. Le tiers des lésions étaient de plus de 5 mm et 14% étaient rehaussantes à l'examen avec gadolinium. Il y avait plus de lésions sus-tentorielles que sous-tentorielles, pour un ratio de 7,5 à 1. Quarante-vingt-quinze pour cent des lésions de la moelle épinière étaient dans la région cervicale et la région thoracique et 34% étaient rehaussantes à l'examen avec gadolinium. Les lésions s'étendaient en moyenne sur une longueur correspondant à  $3,6 \pm 3,3$  corps vertébraux. Cinquante patients (50%) ayant subi une IRM du cerveau et 54 patients (64%) ayant subi une IRM de la moelle épinière avaient une forme optique et spinale de la SEP. À l'IRM, l'apparence et la distribution des lésions des groupes optique-spinal et classique étaient semblables sauf que les patients atteints de la forme optique-spinale avaient moins de lésions cérébrales et des lésions plus longues et plus sévères à la moelle épinière. L'IRM du cerveau et de la moelle épinière des patients Asiatiques atteints de SEP étaient semblables à celles des patients de l'Ouest sauf qu'ils avaient de plus grosses lésions à la moelle épinière.

Can. J. Neurol. Sci. 2006; 33: 95-100

Paraclinical evidence, consisting of evoked potentials study, cerebrospinal fluid analysis or imaging techniques, has been accepted in the diagnosis of multiple sclerosis (MS).<sup>1</sup> Magnetic resonance imaging (MRI), of the brain in particular, is known to be very helpful, with a sensitivity reaching 95%.<sup>2</sup> Various brain MRI lesions were considered specific to MS in patients younger than 50 year-old; among these were periventricular lesions,<sup>2-4</sup> gadolinium enhancement,<sup>4-8</sup> large lesions,<sup>3</sup> ovoid and callosal or sub-callosal lesions,<sup>9-11</sup> and the total number of lesions or lesion

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load.<sup>4,12,13</sup> Barkhof et al<sup>14</sup> showed that the fulfillment of three out of four MRI criteria (gadolinium-enhanced or 9 T2 lesions,  $\geq 3$  periventricular lesions, juxtacortical lesions, and infratentorial lesions) improved the specificity to 78%, and the positive predictive value to 75% in the diagnosis of MS. This became the basis of new diagnostic guideline for MS, where MRI plays a central role.<sup>15</sup>

Spinal cord MRI were less well studied in MS and prospective studies are currently insufficient.<sup>15</sup> Previous studies demonstrated that spinal cord involvement was shown as high intensity lesions on T2 weighted images, well circumscribed and mainly oval,<sup>16</sup> with a predilection for the cervical (49-62%) and thoracic (38-47%) regions.<sup>17-19</sup> Lesions were variable in size: ranges from 0.5 to 6 vertebral body segments longitudinally,<sup>18</sup> or 2-60 mm, and the median size was 10 mm.<sup>16</sup> However, 12.5% of patients had diffuse lesions with a mean size of 11.2 ( $\pm 5.7$ , maximum 19) vertebral segments.<sup>19</sup> The longitudinal axis of the lesions extended along the long axis of the spinal cord.<sup>19</sup> Most patients had one (68%) or two (19-65.4%) lesions<sup>16,19</sup> with a mean of  $1.74 \pm 1.57$ <sup>17</sup> or a median of three<sup>19</sup> lesions per-patient. Most lesions were situated either centrally (16-72%) or posteriorly (18-41%).<sup>16,17</sup> Cord atrophy was seen in 0.8-40%,<sup>16-19</sup> and cord swelling in 2.8-14%,<sup>16,18,19</sup> depending on the method of measurement.<sup>16-19</sup> Gadolinium enhancement was seen in 17.2% of patients.<sup>19</sup>

Although MS is considerably less common in Asia, it has long been noted that there were significant differences compared with Western counterparts. Besides lower prevalence, MS in Asia has higher female preponderance, rare familial occurrence, more severe and frequent optic nerve and spinal cord attacks, resulting in greater functional disability, visual impairment and higher incidence of paroxysmal tonic spasm. Cerebral and cerebellar involvement is less common, especially among patients with the optic-spinal recurrent form, and cerebrospinal fluid oligoclonal bands are less frequently positive.<sup>20-26</sup> These differences are not limited to Asia. Studies from Brazil,<sup>27-28</sup> Kenya,<sup>29</sup> Martinique (French West Indies),<sup>30</sup> black South Africans<sup>31</sup> and Americans of African ancestry<sup>32</sup> have shown similar findings. Magnetic resonance imaging studies in Japan also showed a difference among the patients with disseminated ("Western") versus optic-spinal ("Asian") forms of MS. The disseminated patients had more brain lesions than the optic-spinal patients, more frequent gadolinium enhanced but fewer lesions. In the spinal cord, there was lower frequency of gadolinium enhancement, swollen and atrophied spinal cord. Gadolinium enhancement of the optic tract or nerve, and syrinx-like formation in the spinal cord were seen exclusively in the optic-spinal form of MS. Optic-spinal patients also had longer spinal cord lesions, averaging  $5.8 \pm 3.2$  vertebral segments long.<sup>33,34</sup> To-date, there were few systematic studies to characterize the brain and spinal cord MRI of MS patients elsewhere in Asia. This is a multi-centre regional collaborative study in Asia, to describe the first brain and spinal cord MRI in patients with MS, and compare the MRI of the classical and optic-spinal patients.

## METHODS

We conducted a retrospective survey on the first brain and/or spinal cord MRI done according to clinical indication in seven

regions across Asia (Malaysia, Korea, India, Singapore, Thailand, Taiwan and Hong Kong). The patients were diagnosed to have clinically definite MS according to Poser's criteria.<sup>1</sup> The optic-spinal form of MS was defined as patients with recurrent myelitis and/or optic neuritis clinically, without involvement of other part of the central nervous system. The classical form of MS was seen in patients with clinically disseminated involvement beyond optic nerve and spinal cord. The MRI was done in various centres on at least a 1.5 Tesla machine, with the minimal of T1, T2 and FLAIR weighted images, but preferably with gadolinium enhancement. The spinal cord section was 3 mm or less. The images were read by at least two neuroradiologists/neurologists and the interpretation reached by consensus. Where there was dissenting view, the opinion of a third neuroradiologist/neurologist was accepted as final. The results were collated and analyzed centrally.

Parametric variables were analyzed with ANOVA, and non-parametric with Fisher's exact test, chi square (with Yates' correction when necessary) or Mann-Whitney statistics. All p values of less than 0.05 were accepted as significant.

## RESULTS

### Demography

Of the 136 patients who initially enrolled in the study, 121 patients had sufficient clinical details to be included in the analysis. There were 101 first MRI of the brain and 86 of the spinal cord; 66 of whom had both first brain and spinal cord MRI. On average, the brain MRI was done  $2.9 \pm 6.2$  years, and spinal cord MRI  $3.2 \pm 7.2$  years after the first symptom. The brain MRI was done  $2.2 \pm 4.9$  years and the spinal cord MRI  $2.7 \pm 5.6$  years after the diagnosis. The mean age was  $38 \pm 11$  years, with 100 (87%) female. The ethnic composition consisted of Chinese (47%), Indians (22%), Thais (14%), Koreans (12%), Malays (4%), and Taiwan aborigines (1%). Out of these, 68 (58%) had optic-spinal MS. There was no difference in the age

**Table 1: Demography of classical and optic-spinal multiple sclerosis patients**

	Classical (N=53)	Optic-spinal (N=68)	p values
Age (years)	37 $\pm$ 11	39 $\pm$ 12	NS
Female (%)	82	91	NS
Chinese (%)	39	54	0.04
Course (%)			
Relapsing remitting	36	53	NS
Secondary progressive	3	2	NS
Progressive relapsing	2	1	NS
Primary progressive	3	1	NS

NS = no significance

**Table 2: Brain MRI findings in patients with multiple sclerosis**

	<b>Total (N=101)</b>	<b>Classical (N=51)</b>	<b>Optic-spinal (N=50)</b>	<b>p values</b>
Total no. of lesions/patient	17.0 ± 23.0	25.0 ± 27.0	9.4 + 13.0	<0.001
Cerebral atrophy, no. (%) (N = 84)	21 (25%)	13/42 (31%)	8/42 (19%)	NS*
Location/distribution				
Supratentorial	15.0 ± 20	22.0 ± 24	8.3 + 12.0	<0.001
Periventricular WM**	3.8 ± 5.6	5.5 ± 6.7	2.2 + 3.5	0.011
Deep WM	5.0 ± 8.0	7.2 ± 9.5	2.7 + 5.5	0.006
Juxtacortical WM	5.6 ± 9.6	8.1 ± 12	3.0 + 6.0	0.0033
Corpus callosum	0.8 ± 1.9	1.2 ± 2.5	0.4 + 1.0	NS
Infratentorial	2.0 ± 3.8	3.0 ± 4.8	1.0 + 2.2	<0.001
Cerebellum	0.3 ± 0.7	0.3 ± 0.8	0.3 + 0.6	NS
Midbrain	0.4 ± 1.3	0.5 ± 1.5	0.2 + 1.0	NS
Pons	0.8 ± 2.0	1.3 ± 2.6	0.3 + 0.7	0.0059
Medulla	0.3 ± 0.6	0.5 ± 0.8	0.1 + 0.2	<0.001
Appearance of lesions				
Gadolinium enhancement	2.4 ± 7.4	4.4 ± 10	0.4 + 0.9	0.016
Large (≥ 5 mm)	5.6 ± 12	8.8 ± 15	2.3 + 5.6	<0.001
Oval/ovoid	2.2 ± 4.4	3.2 ± 5.5	1.1 + 2.7	<0.001
Confluent	1.4 ± 4.0	2.3 ± 5.2	0.4 + 1.8	<0.001
Perpendicular	0.2 ± 1.2	0.4 ± 1.7	0.04 + 0.2	NS
Hypointense on T1	3.5 ± 8.1	5.3 ± 10.3	1.6 + 4.3	0.0093
Black hole on T1	0.8 ± 2.2	1.0 ± 2.5	0.7 + 1.9	NS

\*NS = no significance, \*\*WM = White matter. Unless otherwise stated, the numbers are expressed as mean ± sd.

and sex of the classical and optic-spinal groups. Chinese is overrepresented in the optic-spinal group (Table 1).

### Brain MRI

Of the 101 patients, 12% had normal MRI brain. There were on average 17 lesions in the T2 weighted images of brain MRI, most of these were asymptomatic. There were 69 patients (68%) who had four or more lesions on the brain MRI, 50 patients (51%) who had nine or more lesions. There were many more lesions supratentorially than infratentorially, with an average ratio of 7.5 : 1. Almost all of these lesions were located in the white matter, with rare patients (6/101 or 6%) having gray matter lesions (Tables 2 and 3). Most of the lesions were located in the juxtacortical, periventricular and deep white matter. Corpus callosum lesions were less common. Cerebral atrophy was seen in about a quarter of the patients. Infratentorially, about half of the lesions were located in the pons. A third of the lesions were greater than 5mm. The large lesions were typically discrete and ovoid, some of which were confluent. Twenty-one percent of the lesions were hypointense on T1 weighted images, 14% enhanced with gadolinium. Black holes, with the same intensity as cerebrospinal fluid, were seen in 5% of lesions.

Fifty of the 101 patients (50%) had optic-spinal MS. There were significantly more lesions among the classical MS group as

**Table 3: Unusual brain MRI features**

<b>Patient</b>	<b>Age, ethnicity, sex</b>	<b>Type of MS</b>	<b>Brain MRI</b>
1	41, Korean female	Classical	One 3-5 mm cortical lesion, one 3-5 mm basal ganglia lesion
2	41, Malaysian Chinese female	Classical	One 12x16 mm oedematous cortical lesion
3	26, Korean female	Classical	14 cortical lesions, each ≥ 5 mm
4	36, Malay female	Optic-spinal	3 basal ganglia lesions, largest 25 x 8 mm
5	33, Korean female	Classical	Large confluent lesion extending from basal ganglia to the optic chiasm, >35mm
6	34, Korean female	Classical	Large lesion extending from both forceps to the external capsule and the lateral wall of the third ventricle/hypothalamic region.

**Table 4: Spinal cord MRI features**

	<b>Total (N=86)</b>	<b>Classical (N=32)</b>	<b>Optic-spinal (N=54)</b>	<b>p values</b>
Total no. of lesions	120	48	72	
No. of lesions/patient	1.4 ± 1.1	1.5 ± 1.5	1.3 ± 0.8	NS*
Size (no. vertebral bodies)	3.6 ± 3.3	2.5 ± 2.3	4.2 ± 3.6	0.001
No. of large lesions**	56 (47%)	14 (29%)	42 (54%)	0.012
Location				
Cervical	61 (51%)	29 (61%)	32 (44%)	NS
Thoracic	43 (36%)	13 (27%)	30 (42%)	NS
Cervicothoracic	10 (8%)	4 (8%)	6 (8%)	NS
Thoracolumbar	3 (3%)	2 (4%)	1 (1%)	NS
Lumbar or sacral	2 (2%)	0	2 (3%)	NS
Entire spine	1 (1%)	0	1 (1%)	NS
Cross section appearance				
Central	17/101 (17%)	6/41 (15%)	11/60 (18%)	NS
Lateral	61/101 (60%)	32/41 (78%)	29/60 (48%)	0.0052
Complete cross section	23/101 (23%)	3/41 (7%)	20/60 (33%)	0.0048
T1 weighted images				
Gadolinium enhancement	34/99 (34%)	14/39 (36%)	20/60 (33%)	NS
Hypointense lesions	30/104 (29%)	6/39 (15%)	24/65 (37%)	0.034
Black holes (syrinx-like)	3/104 (3%)	0/39 (0%)	3/65 (5%)	NS
Swelling	24/105 (23%)	5/39 (13%)	19/66 (29%)	NS
Atrophy	8/105 (8%)	2/39 (5%)	6/66 (9%)	NS

\*NS = no significance, \*\*Large lesion = lesions larger than two vertebral body segments.

compared to the optic-spinal group (Table 2). Only one classical MS patient had no lesion in the brain MRI (2%), whereas there were 13 patients (26%) in the optic-spinal MS group ( $p=0.0013$ ). There were 43 patients (84%) who had four or more lesions on brain MRI in the classical group, as compared to 26 patients (52%) in the optic-spinal group ( $p=0.001$ ). Similarly, 33 patients (65%) had nine or more lesions in the classical MS group, as compared to 17 patients (34%) in the optic-spinal group ( $p=0.0039$ ). The distribution and appearance of lesions were similar in classical as compared to optic-spinal groups. Patients with classical MS had significantly more lesions than optic-spinal MS in all areas except for corpus callosum, cerebellum and midbrain (Table 2). Both forms of MS had similar numbers of lesions in the cerebellum (Table 2), with nine patients in each group having between one to three lesions in the cerebellum. However, due to the fewer number of lesions elsewhere, the optic-spinal patients had proportionally higher number of lesions in cerebellum (2.8%, 13/468 versus 1.3%, 16/1269,  $p=0.048$ ). Optic-spinal patients were more likely to have cerebellar lesions larger than 5 X 5 mm, though this was not statistically significantly ( $0.8 \pm 1.0$  versus  $0.2 \pm 0.4$  large lesions,  $p=0.14$ ).

Cerebral atrophy was related to total number of lesion or lesion load. Those with cerebral atrophy ( $31 \pm 29$  lesions) had significantly more lesions than those who did not ( $13 \pm 19$

lesions,  $p=0.001$ ). There was more cerebral atrophy among the classical as compared to optic-spinal MS patients. However, this was not statistically significant (Table 2). There were six patients (6%) with unusual brain MRI features which are detailed in Table 3. These patients had gray matter lesions mainly in basal ganglia, hypothalamus and optic chiasm. They were mainly seen among the Korean patients.

### **Spinal cord MRI**

Of the 86 patients, there were all together 120 spinal cord lesions. The lesions were ovoid, well circumscribed and hyperintense on T2 weighted images. There was on average 1.4 lesions per-patient. Ten patients (12%) had no spinal cord lesion, 48 (56%) had one, 20 (23%) had two, seven (9%) had three or more lesions. The average size of the lesions was 3.6 vertebral body segments. Fifty-nine-percent of these lesions were located in the cervical or cervico-thoracic cord, 95% of the lesions were in the cervical and thoracic spinal cord (Table 4). Three fifths of the lesions were situated at the lateral or peripheral aspect of the cord. More than a fifth involved the whole cross section of the cord. A third of the lesions were enhanced with gadolinium, more than a fifth of the lesions were associated with focal cord swelling. More than a quarter was hypointense on T1 weighted images, but only 3% had syrinx-like black holes, and 8% had atrophy (Table 4).

Fifty four patients had optic-spinal MS. These patients had similar number, locations and appearances of lesions as the classical MS patients. However the optic-spinal patients had significantly longer and severe lesions. The later is reflected by more optic-spinal patients with cord swelling, involvement of complete cross section, hypointense lesions, atrophy, and syrinx-like black holes, though only the hypointense lesions were statistical significant (Table 4).

## DISCUSSION

Our study showed that there were many similarities in the appearance of brain and spinal cord MRI in Asian MS patients as compared to those reported from the West.<sup>2-14</sup> The typical appearance of a brain MRI in our patient is one with many T2 hyperintense lesions,<sup>4,12,35</sup> 68% had more than four lesions as suggested by Paty et al<sup>2</sup> and 51% had more than nine lesions as in Barkhof et al.<sup>14</sup> These lesions were almost entirely situated in the white matter, especially in the periventricular,<sup>2-4,14,35</sup> juxtacortical and deep white matters.<sup>14</sup> A third of the lesions were larger than 5 mm.<sup>3</sup> They were typically discrete and ovoid.<sup>9-11</sup> Forteen percent of the lesions enhanced with gadolinium.<sup>4,7,14</sup> There were more supratentorial than infratentorial lesions.<sup>3,14</sup>

There were also many similarities in the spinal cord MRI of our patients and those reported from the West.<sup>16-19</sup> The spinal cord MRI of our patients typically showed eccentric or peripheral well circumscribed T2 hyperintense ovoid lesions, a third enhanced with gadolinium. The lesions were almost exclusively in the cervical and thoracic cord. However, the average size of the spinal cord lesions of our patients was 3.6 vertebral body segments, larger than that seen in Western patients. Long segment spinal cord lesions in MRI has been previously noted in the Asian patients with MS,<sup>20,33,34</sup> though large lesions are not rare among MS patients in the West.<sup>17-19</sup> Twenty-three-percent of our patients had cord swelling, which is higher than 2.8-14% quoted from the West.<sup>16,18,19</sup>

Comparing the optic-spinal with the classical form of MS among our patients, there were also many similarities of MRI lesions between the two groups, in its distribution and appearance. The optic-spinal patients had fewer brain lesions in all locations except the cerebellum. However, even among the optic-spinal group, 52% had four or more lesions, and 34% had nine or more lesions on brain MRI. In the spinal cord, the lesions in the optic-spinal group were larger and more severe. These differences have been noted in the previous studies.<sup>20,33,34</sup>

The similarity in MRI findings between our patients and MS patients in the West, and classical versus optic-spinal MS among our patients, is highly relevant to the recent renewed interest in Devic's disease (neuromyelitis optica). There is a move to redefine Devic's disease and regard it as a distinct disease entity apart from MS, and to lump Asians with optic-spinal MS with the re-formulated Devic's disease.<sup>36,37</sup> This study on the other hand, demonstrated the many similarities between the MRI results of Asian and Western MS patients, and between optic-spinal and classical MS patients among Asians.<sup>20</sup>

## ACKNOWLEDGEMENTS

Our gratitude to Dr B. Ong, National University Hospital and Sero Asia Pacific for their various assistance.

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