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Anatomical Distribution of Central Nervous System Plaques in Multiple Sclerosis: An Iranian Experience

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Abstract: Multiple Sclerosis (MS) begins most commonly in young adults and is characterized by multiple areas of Central Nervous System (CNS) white matter inflammation, demyelination and glial scarring. The most valuable laboratory aid for diagnosing MS is Magnetic Resonance Imaging (MRI). An advanced type of MRI that exploits molecular diffusion can detect acute and active lesions. Early diagnosis and onset of treatment help to hinder disease progression. The aim of this study was to compare the findings of conventional and Diffusion-Weighted (DW) MRI in assessing the cerebral lesions of MS patients. Thirty patients with clinically definite MS (mean age 32.76±8.79 years) and an age- and sex-matched control group of 30 healthy volunteers (mean age 32.75±9.23 years) were enrolled in this 12 month descriptive-prospective survey. Both groups were subjected to conventional and DW MRI and were compared in respect of the total number, morphology, location and the mean size of the intra-cerebral MS plaques. The sensitivities and specificities of both imaging methods in detecting these plaques were determined. The conventional method revealed significantly more plaques within the brain ($p<0.05$) and showed more ovoid lesions. More lesions were detected by the conventional method in the periventricular area, centrum semiovale and corpus callosum. The minimum plaque size was significantly lower in the conventional method group. The sensitivity of both methods was 100%. The specificities of conventional and DW MRI were 86.6 and 96.6%, respectively, so DW MRI may detect lesions that are not obvious by routine methods.

Key words: Intra-cerebral plaque, MRI, diffusion-weighted MRI, descriptive-prospective survey, diagnosis of MS

INTRODUCTION

Multiple Sclerosis (MS), the most prevalent demyelinating disease, which results in non-traumatic nervous system impairment predominantly in young and middle-aged adults and affects more than two million people worldwide (Grossman and Yousem, 2003; Koutsouraki *et al*., 2010), was first described in 1868 by Charcot. The clinical spectrum of MS ranges from symptom-free individuals to those suffering from a rapidly progressive and debilitating disease (Confavreux and Vukusic, 2008). During early stages of the disease the majority of patients suffer from relapsing-remitting symptoms, which gradually develop into permanent debilitating neural symptoms (Rowland, 2000). Chronic MS is characterized by the presence of multiple inflammatory areas in the white matter of the Central Nervous System (CNS) in addition to demyelination and glial sclerosis. Younger women are up to three times more likely to suffer from MS than men although the figures are comparable in older individuals (Tomassini and Pozzilli, 2009). No specific causative agent has been identified; it has been proposed that genetic factors, autoimmune mechanisms, geographical area, exposure to sunlight, nutrition, viral infections and trauma could cause MS (Grossman and Yousem, 2003; Rowland, 2000; Casaccia-Bonnefil *et al*., 2008; Mehta, 2010; Ascherio *et al*., 2010).

No specific clinical diagnostic tests are available for MS, but Cerebrospinal Fluid (CSF) analysis (Frederikson, 2010; Villar *et al*., 2010), Evoked Potential (EP) evaluation (Leocani and Comi, 2008) and MRI have been considered useful techniques in the diagnosis of the disease. Approximately 70% of MS cases present with increased levels of CSF and approximately 90% of MS patients have increased levels of oligoclonals (Grossman and Yousem, 2003; Rowland, 2000; Sutton, 2003; Villar *et al*., 2010). MRI is considered the most accurate imaging technique for

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diagnosing MS and is also more sensitive than EP evaluation or the study of oligoclonal bands (William and Orrison, 1998; Leocani and Comi, 2008). T2 weighted (T2W) imaging is the standard MRI technique. It is very sensitive and provides information regarding the distribution and morphology of MS lesions. However, it can be difficult to distinguish MS lesions from other pathologies such as vascular disease (William and Orrison, 1998). Fluid-Attenuation Inversion Recovery (FLAIR) is an alternative MRI methodology, which is preferred to the T2W technique for the detection of corpus callosum and subcortical MS lesions (Ramli *et al*., 2010). However, FLAIR is inferior to the T2W technique in terms of identifying posterior fossa, brain stem and spinal cord lesions (Grossman and Yousem, 2003; Rowland, 2000). FLAIR and T2W are considered conventional MRI techniques but are reportedly incapable of detecting minimal disease-related changes, particularly in Normal Appearing White Matter (NAWM) tissue. The correlation between conventional MRI findings and the clinical progress of MS in the long term is classed as moderate (Mascalchi *et al*., 2005). Diffusion-Weighted MRI (DW-MRI) is a sophisticated MRI imaging technique designed to overcome the limitations of conventional techniques in the evaluation of MS (Filipi and Agosta, 2009; Zipp, 2009). This technique is based on molecular diffusion and can identify the majority of acute and active MS lesions (Grossman and Yousem, 2003; Rovaris *et al*., 2001). This study was designed to compare DW-MRI and conventional MRI (T2W and FLAIR) techniques in terms of the detection of intracranial MS lesions and data relating to morphology, the number of lesions, size and anatomical location.

MATERIALS AND METHODS

A cross-sectional study of 30 patients diagnosed with MS and 30 healthy age- and sex-matched individuals was carried out by researchers in the Hafez Imaging Center, Tabriz, Iran. Data were gathered from April 2006 to May 2007. Clinical diagnosis of MS was based on the classification system of Poser *et al*. (1983) and patients were considered to be suffering from MS if more than one lesion was identified during neurological examination together with a disease history or a history of two clinical accidents. Evidence of one lesion during neurological examination and the identification of other lesions using MRI or EP were also considered to be positive for MS. Laboratory tests were used to support the clinical diagnosis of MS as determined by the methods of Poser *et al*. (1983). Identification of at least two lesions in the patient's history or during physical examination was considered evidence of MS. However, identification of only one lesion in the patient's history or upon physical examination was not considered sufficient evidence to diagnose MS; detection of at least one lesion using MRI or EP became obligatory. Furthermore, IgG levels and pattern of distribution in the patient's CSF had to be abnormal for MS to be diagnosed (Grossman and Yousem, 2003; Rowland, 2000). Subjects were excluded from the study if they had cardiac pacemakers, intracranial aneurysm clips, implanted electrodes such as nerve stimulators or implanted drug pumps.

Conventional (T2W and FLAIR) and DW-MRI images were obtained using a Signa Exite 2 (GE), 1.5 Tesla, MRI. During T2W imaging, prolonged echo time (TE) and repetition time (TR) were applied (TE = 50-80 m sec, TR = 4000-5000 m sec); during FLAIR imaging, prolonged T1 value, TR and TE were considered (T1 value = 1800-2500 m sec, TE = 110-130 m sec, TR = 8000 m sec). A strong pulsed gradient was used during the MR signal change in DW-MRI imaging; this signal change was made using spin echo or gradient echo by applying the Echoplanar technique. Axial, sagittal and coronal cuts were obtained during conventional MRI (T2W and FLAIR) and DW-MRI for all subjects in the experimental and control groups. Imaging results were interpreted by two experienced neuroradiologists.

Data regarding sex, age and residence (urban, rural and unknown) were collected for all individuals. In addition, the anatomical locations of brain plaques and their numbers in each location (periventricular, centrum semiovale, peduncli cerebellares, hemispherium cerebelli, corpus callosum, subcortical, optic nerve, brain stem and cortex), as well as the sum total, were recorded. The sizes of the smallest and largest brain plaques detected with conventional (T2W and FLAIR) and DW-MRI techniques were obtained. The morphology (ovoid, round, cystic or plaques with mass effect) of MS plaques in the brains of subjects were studied. Brain MS plaques detected using the DW-MRI technique but not with conventional MRI techniques were examined with regard to their anatomical location. This research was carried out with the permission of the Tabriz University of Medical Science ethical board and written informed consent was obtained for every patient.

Data are shown as Mean±SD. A t-test (paired and independent samples) was carried out for the comparison of variables and Spearman rank correlation coefficients were used to evaluate the correlation between conventional MRI findings and results from DW-MRI concerning the anatomical location of lesions in MS patients. A p-value less than 0.05 was considered

statistically significant. SPSS 13.0 (SPSS INC., Chicago, Illinois, USA) was used for all statistical calculations.

RESULTS

Thirty patients, 11 (36.7%) men and 19 (63.3%) women, ranging from 18 to 49 years of age (mean 32.76±8.79 years) were included in the study. A group of 30 healthy individuals (10 men, 20 women), ranging from 15 to 51 years of age (mean 32.75±9.23 years) was included as a control group.

MRI findings in patients: During the DW-MRI study of the patients' brains, 523 plaques were identified. The average number of brain plaques identified in a single patient was 17.43±16.91, ranging from two to 69 in individual cases. The anatomical locations of these plaques were: 260 (49%) identified in the periventricular region, 201 (38%) in the centrum semiovale region, 4 (0.7%) in the peduncli cerebellares, 29 (5.5%) in the hemispherium cerebelli, 24 (4.5%) in the corpus callosum and 4 (0.7%) in the subcortical region. Of the 523 plaques identified using DW-MRI, 133 (25%) had an ovoid shape, 387 (74%) were round, two (0.4%) were cystic and one (0.2%) had a mass effect.

Using conventional T2W MRI to study the patients' brains, 1255 plaques were identified. The average number of plaques identified in a single patient using this technique was 41.83±29.43 and the range in individuals was from three to 69. Of the 1255 plaques identified using T2W MRI, 715 (57%) were periventricular, 413 (33%) were identified in the centrum semiovale region, five (0.4%) in the peduncli cerebellares, 30 (2.4%) in the hemispherium cerebelli, 84 (6.7%) in the corpus callosum and 8 (0.6%) in the subcortical region. Three (0.24%) plaques were located in other regions; two in the pons and one in the optic nerve region. Using this technique, 883 (70.4%) plaques were identified as having an ovoid shape, 360 (28.7%) as being round, 10 (0.8%) as cystic and one (0.08%) having a mass effect.

FLAIR imaging revealed 1328 plaques in a study of the patients' brains. The average number of plaques in a single patient was 44.26±28.57, ranging from six to 41 in individual cases. Of the 1328 plaques detected using this technique, 747 (56%) were in the periventricular region, 413 (31%) in the centrum semiovale region, five (0.4%) in the peduncli cerebellares, 23 (1.7%) in the hemispherium cerebelli, 90 (6.7%) in the corpus callosum and seven (0.5%) in the subcortical region. Two (0.15%) plaques were located in other regions; one was in the pons and one in the optic nerve region. The FLAIR imaging technique identified 923 (68.9%) plaques as being ovoid in shape, 389 (29.3%) as round, 15 (1.1%) as cystic and one (0.7%) plaque with a mass effect.

The average numbers of plaques in single patients, using the different imaging techniques, are summarized in Table 1. The average numbers of brain plaques in a single patient in the periventricular, centrum semiovale and corpus callosum regions were higher using conventional techniques (T2W and FLAIR) than using the DW-MRI technique. However, there was no statistical difference in the number of plaques within each of the regions identified between the various imaging techniques. The average numbers of brain plaques with regard to their morphology in the experimental group are summarized in Table 2. The average number of ovoid plaques identified using conventional techniques was higher than with the DW-MRI technique. There was no statistical difference in

Table 1: Average No. of plaques with regard to their anatomical location using conventional (T2W and FLAIR) and DW-MRI techniques in MS patients

	DW-MRI	T2W imaging technique		FLAIR imaging technique	
Anatomical location	Average No. of plaques for a single patient	Average No. of plaques for a single patient	p-value	Average No. of plaques for a single patient	p-value
Periventricular	8.66±8.53	23.83±17.87	<0.001	24.90±17.74	<0.001
Centrum semiovale	6.70±7.41	13.76±11.74	<0.001	15.23±11.66	<0.001
Peduncli cerebellares	0.13±0.34	0.16±0.59	0.791	0.16±0.59	0.791
Hemispherium cerebelli	0.96±2.82	1.00±1.91	0.957	0.76±1.54	0.735
Corpus callosum	0.80±1.24	2.80±2.13	<0.001	3.00±2.30	<0.001
Subcortical	0.13±0.34	0.20±0.78	0.354	0.23±0.77	0.521
Others	0	0.10±0.20	0.083	0.06±0.25	0.161

Table 2: Average No. of brain plaques with regard to their morphology using conventional (T2W and FLAIR) and DW-MRI techniques in MS patients

	DW-MRI	T2W imaging technique		FLAIR imaging technique	
Morphology of plaques	Average No. of plaques for a single patient	Average No. of plaques for a single patient	p-value	Average No. of plaques for a single patient	p-value
Ovoid	4.43±3.88	29.43±20.48	<0.001	30.76±17.74	<0.001
Round	12.90±13.52	12.00±8.88	0.676	12.96±8.63	0.975
Cystic	0.06±0.25	0.33±1.64	0.333	0.50±1.71	0.136
Lesion with mass effect	0.03±0.18	0.03±0.18	0.333	0.03±0.18	0.136

Table 3: Average size of the smallest and largest brain plaques in millimeters (mm) detected in MS patients using various MRI techniques

	*DW-MRI	T2W imaging technique		FLAIR technique	
Size of plaques	Average plaque size (mm)	Average plaque size (mm)	p-value	Average plaque size (mm)	p-value
The smallest sized plaques detected	3.37±1.75	2.28±1.22	0.007	2.52±2.46	0.130
The largest sized plaques detected	13.85±10.02	13.45±6.53	0.763	14.59±7.69	0.414

*DW-MRI: Diffusion Weighted MRI

the number of plaques with other shapes identified with conventional and DW-MRI techniques. The average number of brain plaques identified by T2W and FLAIR was greater than using the DW-MRI technique ($p<0.05$).

The average sizes of the smallest brain plaques identified in the experimental group using different imaging techniques were as follows: 3.37±1.75 mm using DW-MRI, 2.28±1.22 mm using T2W and 2.52±2.45 mm using the FLAIR technique. The average sizes of the largest brain plaques in the experimental group using different imaging techniques were: 13.85±10.02 mm using DW-MRI, 13.45±6.53 mm using T2W and 14.59±7.69 mm using the FLAIR technique. All findings regarding the sizes of brain plaques using different techniques are summarized in Table 3. There was no statistical difference between the T2W and DW-MRI techniques in terms of detecting the largest brain lesions and the FLAIR and DW-MRI techniques were comparable in terms of the detecting the largest and smallest brain lesions.

MRI findings in the control group: In the control group, four of the 30 individuals were identified as having brain plaques using conventional MRI techniques. However, only one individual with a single plaque was identified using the DW-MRI technique. Control group evaluation using the DW-MRI technique revealed four brain plaques. Two of these plaques were located in the periventricular region and two in the centrum semiovale region; each had a round shape. The smallest plaque measured 1 mm and the largest one measured 4 mm. T2W imaging of the control group revealed 43 plaques; 17 (39%) in the periventricular region and 26 (61%) in the centrum semiovale region. No plaques were identified in other anatomical regions using this technique. Of the 43 brain plaques identified by T2W, 21 (49%) were ovoid in shape and 22 (51%) had a round shape. Two of the plaques measured approximately 1.5 mm and the average size of the largest plaques identified using the T2W technique was 4.6±0.14 mm (range from 4.5 to 4.7 mm). The results obtained using the conventional MRI techniques to study the control group were comparable. DW-MRI revealed 63 plaques in the control group that were not detected using conventional MRI techniques. Of these 63 plaques, 22 (35%) were identified in the periventricular region, 14 (22.2%) in the centrum semiovale region, 3 (4.7%) in the peduncli cerebellares, 23 (36.5%) in the hemispherium cerebelli and one (1.6%) in the subcortical region. One detectable plaque in the periventricular region was identified using DW-MRI but not conventional techniques.

Regarding the total number of brain plaques detected in the experimental and control groups, a significant correlation was evident between the results from DW-MRI and T2W ($r = 0.619$, $p<0.001$) and between DW-MRI and FLAIR ($r = 0.592$, $p<0.001$). There was no significant correlation between the DW-MRI and T2W findings in terms of the smallest brain plaques found in the experimental and control groups ($r = 0.257$, $p = 0.170$) or between the results of DW-MRI and FLAIR ($r = 0.215$, $p = 0.254$). A significant correlation was evident between the DW-MRI and T2W findings ($r = 0.786$, $p<0.001$) and between the results of DW-MRI and FLAIR ($r = 0.845$, $p<0.001$) in terms of detecting the largest brain plaques.

Morphology of brain plaques in MS patients: There was a significant correlation between the DW-MRI and T2W findings regarding the ovoid ($r = 0.675$, $p<0.001$), round ($r = 0.494$, $p<0.05$) and cystic ($r = 0.482$, $p<0.05$) plaques and plaques with mass effect ($r = 1$, $p<0.05$. There was significant correlation between the DW-MRI and FLAIR results regarding the shapes of brain plaques: ovoid ($r = 0.703$, $p<0.001$), round ($r = 0.536$, $p<0.05$), cystic ($r = 0.619$, $p<0.001$) and plaques with mass effect ($r = 1$, $p<0.05$).

Number of brain plaques in different anatomical regions in MS patients: A comparison of conventional MRI findings and DW-MRI results based on the anatomical location of lesions is summarized in Table 4. There was a significant correlation between the DW-MRI and T2W results in the centrum semiovale and subcortical regions and a weak correlation was observed in corpus callosum lesions. Comparison of the DW-MRI and FLAIR results demonstrated a significant correlation between these techniques in the centrum semiovale region and a weak correlation in corpus callosum lesions.

Sensitivity and specificity of MRI techniques: Evaluation of brain lesions in 30 MS patients using DW-MRI and conventional techniques revealed no false negative brain plaques. One false positive plaque was detected using DW-MRI in the control group; four false positive results

Table 4: Comparison of conventional MRI (T2W and FLAIR) findings and DW-MRI results; correlations based on anatomical location of lesions in MS patients

	*T2W imaging technique		**FLAIR imaging technique	
Anatomical location	***Spearman correlation coefficient (r)	p-value	Spearman correlation coefficient (r)	p-value
Periventricular	0.324	0.080	0.346	0.061
Centrum semiovale	0.523	0.003	0.514	0.004
Peduncli cerebellares	0.185	0.328	0.185	0.328
Hemispherium cerebelli	0.201	0.286	0.261	0.163
Corpus callosum	0.432	0.017	0.381	0.038
Subcortical	0.586	0.001	0.125	0.511

*T2W: T2 Weighted imaging MRI; **FLAIR: Fluid attenuated inversion recovery; ***r coefficient more than 0.5 was considered powerful

were obtained using conventional techniques. From the results of this study, we conclude that the sensitivity of DW-MRI and conventional techniques (T2W and FLAIR) in the detection of MS brain lesions is approximately 100%. However, the specificity is approximately 96.6 and 86.6% for DW-MRI and conventional techniques, respectively.

DISCUSSION

Larsson *et al.* (1992) reported an increased diffusion coefficient in MS lesions identified by T2W imaging, using DW-MRI. Several quantitative studies have investigated the value of DW-MRI in the diagnosis and pathology of MS (Wilson *et al*., 2001; Schmierer *et al*., 2004). As far as we are aware, this is the first study comparing the qualitative findings of conventional MRI and DW-MRI in MS patients.

Since it was first introduced, several studies using DW-MRI have revealed increased diffusivity in apparently healthy brain white matter (NAMW), implying that the technique has greater sensitivity than other varieties of MRI (Filippi and Inglese, 2001; Christiansen *et al*., 1993; Werring *et al*., 1999; Kidd *et al*., 1999; Bammer *et al*., 2000; Filippi *et al*., 2000; Rovaris *et al*., 2001; Filipi and Agosta, 2009; Zipp, 2009). Nusbaum *et al*. (2000) showed that the average increase in diffusivity was greater in secondary progressive MS lesions than in other parts of the brain. It is therefore striking that although the present study confirms the high specificity of DW-MRI, the technique identified fewer lesions than conventional MRI.

There are three possible explanations for this finding. First, although qualitative evaluation (diffusion measurement) of white matter lesions in apparently normal brain tissue has revealed obvious differences, these differences are not sufficient to provide quantitative information for interpretation. DW-MRI may identify lesions undetected by conventional MRI, but it may not be possible to use these data for imaging purposes. Secondly, some research suggests that conventional MRI is not specific enough to evaluate brain lesions in MS patients, so there may be false positive results (Rowland, 2000). Thirdly, DW-MRI accurately detects acute MS lesions whereas conventional MRI detects both acute and chronic MS lesions. Therefore, more lesions are identified by conventional methods (William and Orrison, 1998).

Quantitative DW-MRI is more accurate in detecting primary stages of brain inflammation and evaluating the nature of brain lesions in MS patients than conventional MRI (Filippi and Rocca, 2003; Filippi, 2001), revealing subtle changes in NAMW invisible to the conventional technique (Rovaris *et al*., 2001) and possibly identifying smaller MS lesions. In this study, there was a correlation between the largest MS plaques of the brain using conventional and DW-MRI, but DW-MRI was not superior to conventional techniques in detecting the smallest plaques. Indeed, conventional MRI could detect smaller MS plaques more reliably than DW-MRI, which conflicts with previous research findings. The lower specificity of conventional MRI could explain this result, implying that some lesions detected by conventional MRI are false positives (Rowland, 2000). More research is required to elucidate the differences found with qualitative and quantitative studies.

Filippi and Inglese (2001) compared the morphology of lesions identified by conventional and DW-MRI in patients with ischemic brain lesions and concluded that DW-MRI was more accurate. Most studies, using conventional MRI, have demonstrated that most MS lesions are oval (Grossman and Yousem, 2003) and our data are consistent with this conclusion. We found no significant differences in MS brain plaque morphologies between the two MRI techniques. However, more oval MS brain lesions were detected with conventional MRI than DW-MRI. There are two possible explanations for these findings. First, more plaques were identified with the conventional technique, so most of the plaques identified were oval. Secondly, the quality of the images obtained differs between the two techniques and this could affect how oval and round lesions are interpreted by radiologists; lesions that are considered oval using conventional techniques could be interpreted as round using DW-MRI. More studies are needed to clarify this

issue; post mortem studies and comparison of results with imaging findings are advised (Filippi and Inglese, 2001).

In MS patients the gray matter diffusivity coefficient has been reported to be greater than that of normal brain (Cercignani *et al*., 2001) and this is more apparent using DW-MRI than conventional MRI (Schmierer *et al*., 2004; Fabiano *et al*., 2003). Horsfield (2001) highlighted that MS, in addition to its multifocal nature, is a diffuse white matter disease and/or white matter in the proximal and distal areas of visible lesions undergoes Wallerian degeneration, as detected by conventional MRI (T2W). On the basis of this finding and other studies, quantitative DW-MRI could be better at detecting gray matter lesions than conventional techniques, in addition to its ability to detect NAWM diffusivity problems (Filippi and Inglese, 2001; Horsfield *et al*., 1996; Christiansen *et al*., 1993; Werring *et al*., 1999; Bammer *et al*., 2000; Filippi *et al*., 2000; Filippi and Rocca, 2010; Calabrese *et al*., 2010). Present findings suggest that DW-MRI is comparable to conventional techniques in the detection of MS lesions in various locations in the brain.

Present results are consistent with earlier reports that the sensitivity of conventional MRI in detecting MS lesions in the brain is between 85 and 100% (Sutton, 2003; William and Orrison, 1998) and that the sensitivities of conventional MRI and DW-MRI are about equal (Grossman and Yousem, 2003; Rowland, 2000); we found a sensitivity of approximately 100% for both techniques. DW-MRI is held to have higher pathological specificity in detecting MS brain lesions in situ (Rovaris *et al*., 2001; Filippi and Grossman, 2002; Mathiesen *et al*., 2002). In agreement with other studies, the specificity of DW-MRI was higher (96.6%) than conventional MRI (86.6%) in the present study.

Of the 523 plaques identified by DW-MRI in our study, 63 were not observed using conventional MRI, presumably indicating the higher sensitivity of DW-MRI in detecting NAWM lesions in the brains of MS patients. Diffusivity changes in the white matter of MS patients are only detectable using DW-MRI. Detection of these lesions is very important, especially in those patients who have clinical and paraclinical findings indicative of MS even when conventional MRI detects no MS lesions. Therefore, DW-MRI could aid in the early detection of MS lesions during the primary development stages of the disease, which could help to prevent permanent sequelae in the Central Nervous System (CNS) and reduce the severity and frequency of future MS attacks.

CONCLUSION

Conventional MRI and DW-MRI are comparable in detecting MS plaques in the brain. However, DW-MRI has higher specificity than conventional techniques. Regarding morphology, size, anatomical location and the number of brain plaques detected in MS patients, DW-MRI was not superior to conventional MRI. Conventional MRI identified more oval shaped plaques than DW-MRI and detected more plaques in the periventricular, centrum semiovale and corpus collosum regions. Furthermore, it was superior to DW-MRI in terms of identifying subtle [small] plaques. However, DW-MRI can detect MS brain plaques that are not revealed using conventional MRI.

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