

The effectiveness of magnetization transfer technique in the evaluation of acute plaques in the central nervous system of multiple sclerosis patients and its correlation with the clinical findings

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PURPOSE

To determine the value of magnetization transfer (MT) imaging in the evaluation of acute plaques, which cause clinical findings in the brain magnetic resonance (MR) images of patients with relapsing-remitting multiple sclerosis, and its correlation with the clinical findings.

MATERIALS AND METHODS

Forty patients with relapsing-remitting multiple sclerosis were included in the study. They were being followed-up for the diagnosis of relapsing-remitting multiple sclerosis based on McDonald's criteria. To evaluate the acute plaques of the patients, their T1-weighted spin echo sequences were divided into 3 groups: precontrast and postcontrast MT images (group 1), postcontrast MT images only (group 2), and precontrast and postcontrast non-MT images (group 3). The sensitivity and positive predictive values were calculated to determine the correlation between the patients considered to have had attacks and the acute plaques detected during MR imaging examinations with T1-weighted spin echo.

RESULTS

After clinical examinations, in 25 of 40 patients (62.5%), there were neurological findings suggesting acute attacks. Among the 3 imaging groups, there was a significant difference in the number of acute plaques. In group 1 there were a total 30 findings suggesting acute plaques; in group 2 33; and in group 3 there were 20. When the correlation between the patients who were considered to have had attacks after their clinical examinations and the acute plaques detected with T1-weighted spin echo examinations were evaluated, the sensitivity and positive predictive values were 97% and 100% in group 1, 87% and 78% in group 2, and 65% and 100% in group 3, respectively.

CONCLUSION

In MS, T1-weighted MT examinations yield more reliable results for following up the treatment and changes in the development of the disease. They also offer a more effective evaluation of the acute plaques that cause clinical findings.

Key words: • multiple sclerosis • brain • magnetic resonance imaging • magnetization transfer

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Multiple sclerosis (MS) is a chronic, demyelinating, degenerative disease, which generally starts in young adulthood in the central nervous system (CNS). It is caused by genetic and environmental factors acting upon autoimmune mechanisms, and progresses with recurrent, functional neurological disorders. Despite a wealth of studies, no single method for definitive diagnosis of MS has been found, and as such, it remains a difficult disease to diagnose. Two of the most important features of the disease are its progression with attacks and the appearance of CNS lesions that appear at various times in varying white matter locations. One of the most objective criteria for diagnosis of MS, as in many other diseases, is the radiological imaging of CNS lesions. Among the medical imaging methods of the CNS, magnetic resonance (MR) imaging is the only method for specific imaging of demyelinating plaques (1). With the new MR imaging techniques developed in recent years, more detailed data have been acquired about the pathological baseline of MS plaques. Magnetization transfer (MT), which is one of these techniques, provides enhanced evaluation of the acute plaques that cause the clinical findings of MS and important data about the pathological baseline of the disease with quantitative measurements (2, 3).

The purpose of this study was to determine the value of MT imaging in the evaluation of acute plaques, which cause clinical findings in the brain MR images of patients with relapsing-remitting MS and its correlation with the clinical findings.

Materials and methods

Forty patients (30 females, 10 males) who were followed up for the diagnosis of relapsing-remitting MS based on McDonald's criteria (4) and were seen in the neurology department between December 2003 and June 2004 were included in the study. All the patients were examined by neurologists. We recorded each patient's age, age at disease onset, duration of the disease, initial findings of the disease, neurological examination findings, follow-up time, and number of total and per year attacks. The affected functional systems were determined according to the expanded disability status scale (5). Neurological defects lasting a minimum of 24 hours were accepted to represent an acute attack, depending on either subjective expressions or objective observation. Symptoms resulting from infection, which increases body temperature, were considered to be "false attacks" (4). Patients who were considered to have had acute attacks (relapse) or to be recovering from an acute attack (remission) after clinical examinations underwent routine brain MR examinations.

Brain MR imaging examinations were performed in a 1.5 T superconductive magnet MR device (Magnetom Symphony Class Maestro,

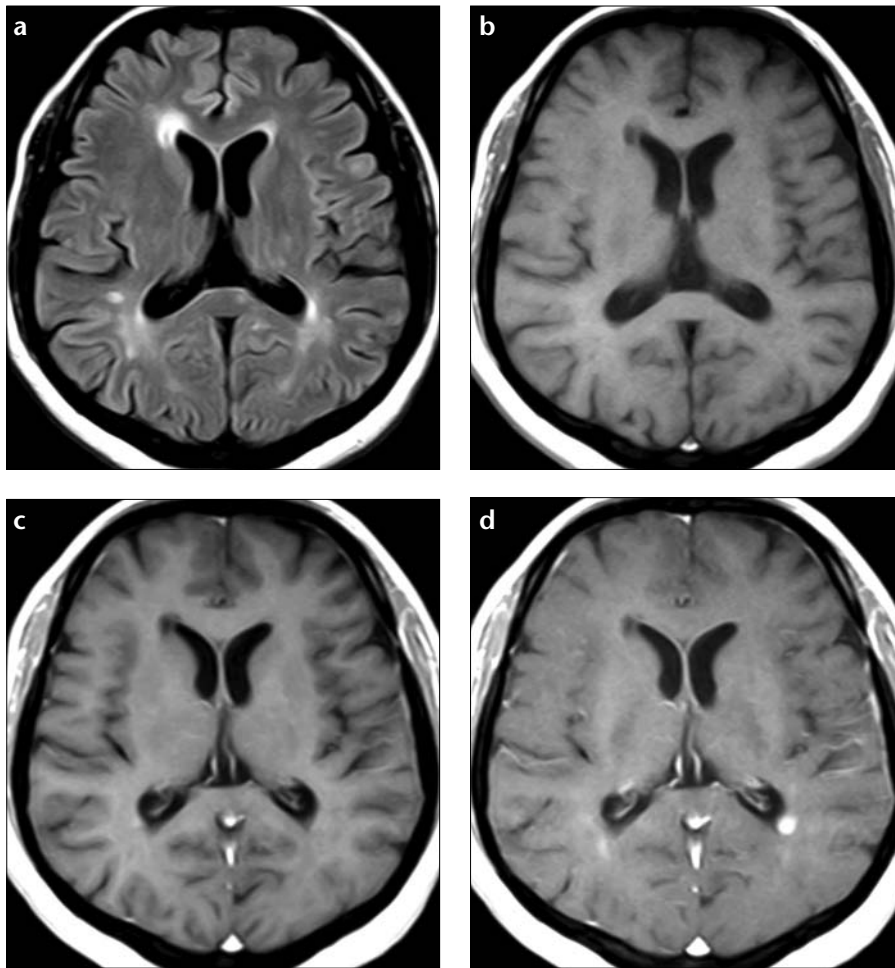


Figure 1. a-d. Millimetric MS plaque adjacent to the left lateral ventricle atrium which is hyperintense in transverse FLAIR (a) and isointense in transverse precontrast non-MT MR images in a 40-year-old female patient (b). There is no pathological enhancement in the plaque area in transverse postcontrast T1W non-MT MR image (c), but there is homogenous enhancement in this area in transverse postcontrast T1W MT MR image (d).

Siemens, Erlangen, Germany), with a 6-channel standard head coil, field of view (FOV) 24 cm, and matrix 256x256. According to our conventional MR imaging protocol, sagittal and transverse T2-weighted (T2W) spin echo (SE) (TR: 5710 msec, TE: 103 msec, NEX: 2, slice thickness: 5 mm, slice interposition: 0.5 mm, examination duration: 1.20 minutes), transverse proton density (PD) (TR: 3270 msec, TE: 14 msec, NEX: 2, slice thickness: 5 mm, slice interposition: 1.5 mm, examination duration: 2.30 minutes), and fluid attenuated inversion recovery (FLAIR) (TR: 9000 msec, TE: 114 msec, TI: 2500 msec, NEX: 2, slice thickness: 5 mm, slice interposition: 1 mm, examination duration: 4.20 minutes) sequences were applied. T1W SE sequence (TR: 500 msec, TE: 7.7 msec, slice thickness: 5 mm, slice interposition: 1 mm, ex-

amination duration: 4.20 minutes) in coronal and transverse planes was performed twice, before and after injection of 0.1 mmol/kg paramagnetic contrast material (Gadolinium-DTPA, Magnevist, Schering, Germany). Precontrast and postcontrast T1W sequences were performed with and without MT. In order to prevent time effect on contrast enhancement, 20 of the T1W examinations were started with MT and the other 20 without MT.

Lesions were initially observed with precontrast examinations in sagittal, coronal, and transverse planes. Subsequently, for evaluation of plaques, which cause clinical findings, T1W SE sequences were divided into 3 groups: precontrast and postcontrast MT images (group 1), postcontrast MT images (group 2), and precontrast and postcontrast non-MT images (group 3).

Two investigators evaluated all of the images prospectively, and a consensus was reached on the findings. In patients who were considered to have had attacks based on clinical examinations, sensitivity and positive predictive values were calculated in order to evaluate the correlation of acute plaques that were determined in T1W SE sequences between three study groups.

Statistical analysis was made with Wilcoxon signed rank test, using "SPSS 13.0 for Windows" and $p < 0.020$ was accepted to be the level of statistical significance.

Results

Ages of the study patients were between 20 and 47 years (mean, 33.2 years), and duration of disease was between 3 months and 15 years (mean, 6.5 years). The expanded disability status scale values of the patients were between 1 and 8 (mean, 2.86).

Following clinical examinations, in 25 of 40 (62.5%) patients, there were neurological findings suggesting an acute attack had been experienced. Among the brain MR imaging of the three groups, T1W SE sequences revealed a significant difference in the number of contrast enhancing acute plaques ($p < 0.020$). The number of images consistent with acute plaques was 30 in group 1, 33 in group 2, and 20 in group 3. Images from one patient in group 1 (who was considered to have had an acute attack according to clinical examinations) revealed no findings consistent with acute plaques. Five hyperintense appearances that were evaluated to be acute plaques in group 2 were later determined to be artifacts secondary to false enhancement due to MT technique when examined with precontrast MT images. A total of 10 acute plaques, which were not detected in group 3, showed homogenous enhancement in postcontrast MT images (Figure 1). Among the acute plaques found in group 1, 15 were in periventricular white matter, 10 were in the centrum semiovale, three were in the cerebellar pedicle, and two were in the corpus callosum (Figure 2). Among the acute plaques, which were not detected in group 2, five were in periventricular white matter, two were in the centrum semiovale, two were in the corpus callosum, and one was located in the cerebellar pedicle (Figure 3).

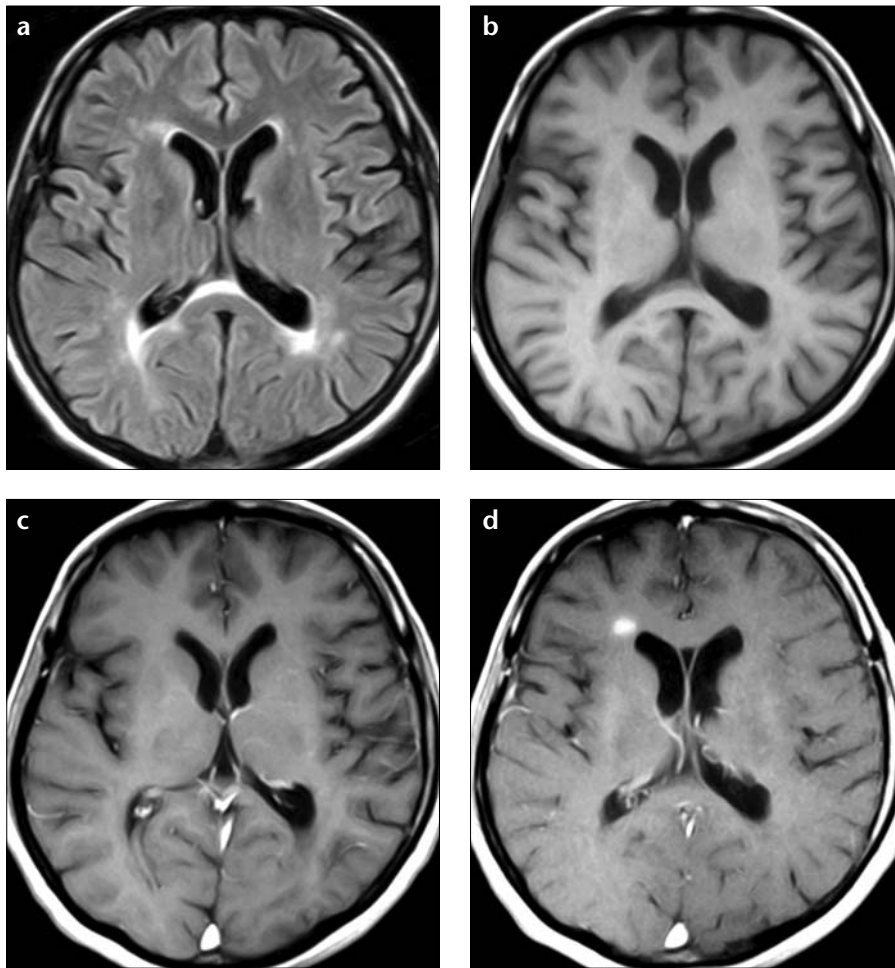


Figure 2 a-d. Millimetric MS plaque adjacent to the right lateral ventricle frontal horn which is hyperintense in transverse FLAIR (a) and mildly hypointense in transverse precontrast non-MT MR images in a 42-year-old male patient (b). There is no pathological enhancement in the plaque area in transverse postcontrast T1W non-MT MR image (c), but there is homogenous enhancement in this area in transverse postcontrast T1W MT MR image (d).

In two of 15 patients who were considered to be remitting after clinical examinations, three suspected hyperintense appearances were observed in white matter adjacent to the lateral ventricle in postcontrast MT images, but when precontrast MT images were evaluated, the hyperintense appearances were understood to be artifacts secondary to the MT technique. In 15 patients' postcontrast MT images, there were not any pathologically enhancing lesions.

When the correlation between the patients who were considered to have had attacks after their clinical examinations and the acute plaques detected with T1W SE examinations of all three groups was evaluated, the sensitivity and positive prediction values were 97% and 100% in group 1, 87% and

78% in group 2, and 65% and 100% in group 3, respectively.

In routine brain MR examinations of all of patients, except for acute plaque areas, there were multiple, hyperintense (some of them with a tendency to coalescence), demyelinating foci in the white matter areas. These were determined to be inactive, chronic gliotic areas.

Discussion

MS is important because of its notable prevalence among neurological diseases, chronic progress, and the fact that it affects young adults. The high morbidity rate of MS contributes to its importance among neurological disorders in young adults in advanced countries (6). Twenty percent of patients become bedridden and another 20% depend on

wheel chairs 15 years after disease onset.

Despite technological advances in diagnostics, no single method for definitive diagnosis exists. Therefore, diagnosis of MS through the correlation of clinical, laboratory, and imaging findings is still the most widely accepted approach. The most effective modality for radiological imaging of lesions is MR imaging, which is one of the most objective tools for the diagnosis (1).

The lesions in MS are subdivided into two types: acute and chronic plaques, according to the stage of the disease. As the treatment plan changes along with the stage of the disease, discrimination of plaques with MR examination is very important. Based on the results of long-term studies and clinical experience, the existence of just one contrast-enhancing lesion is considered to be enough to start treatment (7).

Contrast enhanced T1W examinations are known to be superior to both clinical and non-contrast (PD and T2W) examinations in determining MS activity (8). There are several methods used to improve observation of contrast enhanced acute plaques in T1W examinations. One of these methods is to increase the dose of contrast material (0.1-0.5 mmol/kg), but this is an expensive method (9).

Another method is to increase the time between injection and image acquisition (i.e., 20-30 min. after contrast material injection) in order to increase the contrast material's effect in the extracellular region. This is just as effective as increasing the contrast material dose, but it also increases examination duration (10, 11). Other methods include examination with 3 mm slice thickness, without interposition (12), and to obtain contrast enhanced T1W sequences with MT technique (3, 13).

Magnetization transfer technique has been used as an important critical MR technique to determine potential changes in myelin since 1995. In this technique, real magnetic properties of tissues are affected and contrast/noise ratio is increased instead of contrast material kinetics (3). The proper radiofrequency prepulse at the beginning of the examination selectively saturates protons in tissue proteins, cell membranes, and protons bound to other macromolecules in the water proton pool. Because the main radiofrequency pulse can not stimulate the saturated

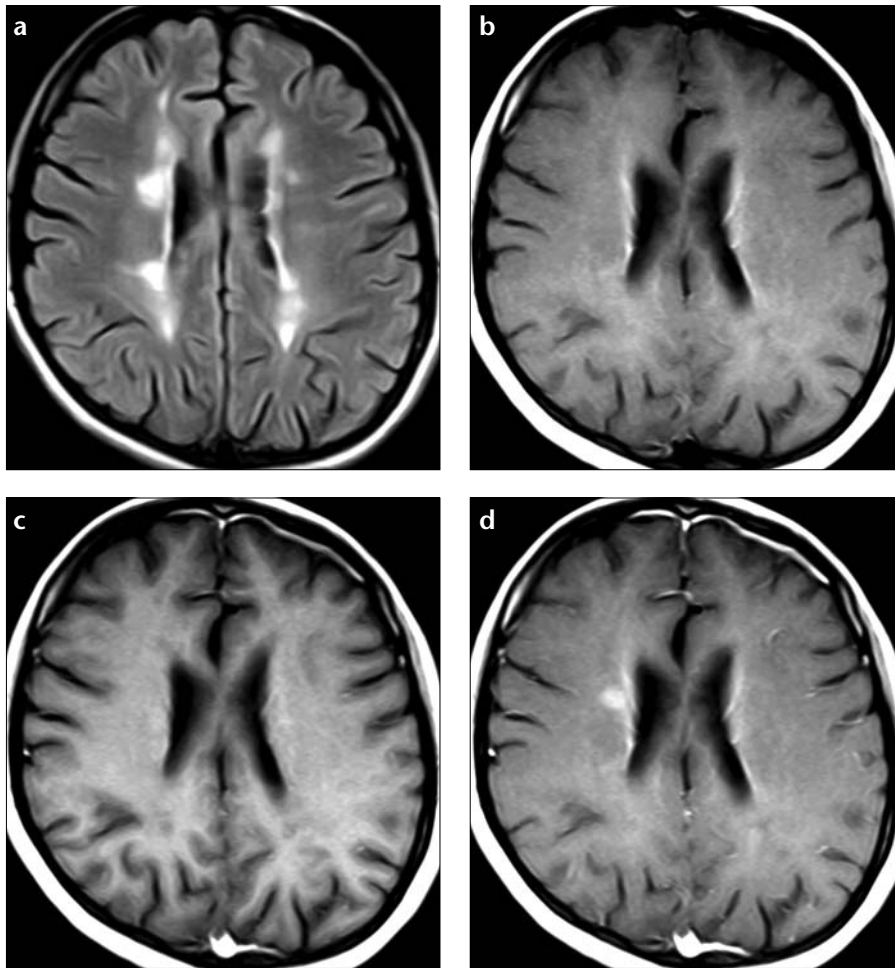


Figure 3 a-d. Millimetric MS plaque adjacent to the right lateral ventricle which is hyperintense in transverse FLAIR (a) and isointense in transverse precontrast non-MT MR images in a 40-year-old, female patient (b). There is indistinct enhancement in the plaque area in transverse postcontrast T1W non-MT MR image (c), but homogenous enhancement in this area in transverse postcontrast T1W MT MR image (d). Also, there is linear signal increases adjacent to both lateral ventricles in pre- and postcontrast MT images secondary to artifacts due to the examination technique.

protons, adequate echo can not be collected from normal tissues and these areas are seen as hypointense (2, 3). Because of the high concentration of macromolecules in myelin, this affect is quite prominent in white matter in the brain. Also, with this technique T1 relaxation time reduction effect of contrast material in pathologically enhancing tissues becomes more prominent and these areas appear to be more hyperintense than in examinations without MT. Owing to these properties of the technique, in contrast enhanced T1W examinations, the contrast/noise ratio between pathological and normal tissues that show signal decrease as well as the enhancement of the lesions becomes more prominent (2, 10, 13). Finelli et al. showed that signal intensity of enhancing pathological lesions

increases 10% and contrast/noise ratio increases 108% with MT technique (13). In a study of 31 patients, Gaura et al. showed that the number of pathologically enhancing acute plaques was a total of 65 in T1W MT and a total of 52 in T1W non-MT images. In T1W non-MT images, a total of 13 acute plaques in 7 patients were not detected, and those patients were considered to be remitting (2).

The major problem in examinations with MT technique is that signal increases in T1W images, which are similar to pathological enhancement, can be seen. For this reason, in evaluation of active lesions seen in many diseases, including MS, false positive results are high and positive predictive value is low with MT technique (3, 10). However, these signal increases almost

always can be seen in precontrast MT examinations, and this makes discrimination easier (3). For this reason, either pre- or postcontrast MT images should be evaluated together (3), or subtracted new images should be formed (2). Sardanelli et al. showed in a study including 10 relapsing-remitting MS patients that in the group in which pre- and postcontrast MT images were evaluated together, a total of 52 acute plaques were found, the examination sensitivity was 96%, and the positive predictive value was 100% (3). However, in the group in which only postcontrast MT images were evaluated, a total of 50 acute plaques were found, and the examination sensitivity was 93%, with a positive predictive value of 73% (3). Gaura et al. observed a total of 52 acute plaques in the evaluation of postcontrast T1W non-MT images and a total of 62 signal increases consistent with acute plaques in images formed by subtraction of pre- and postcontrast T1W non-MT images (2).

In group 1 of our study, pre- and postcontrast MT images evaluated together revealed a total of 30 appearances consistent with acute plaques, while in group 2 only postcontrast MT images were evaluated revealing a total of 33, and in group 3 only postcontrast non-MT images were evaluated, and a total of 20 were detected. When the correlation between the patients who were considered to have had attacks after clinical examinations and the acute plaques detected with T1W spin echo examinations were evaluated, the sensitivity and positive predictive values were 97% and 100% in group 1, 87% and 78% in group 2, and 65% and 100% in group 3, respectively. Eight hyperintensities that were thought to be acute plaques in evaluation of only postcontrast MT images (group 2) were determined to be secondary to artifacts due to examination technique when pre- and postcontrast MT images (group 3) were evaluated together.

In previous studies, subtraction technique was proven to be more useful in non-MT images than MT images, and that in order to subtract without artifacts, patients need to be absolutely motionless and slices should pass exactly from the same level, which turns out to be a restricting factor for the use of this technique (2, 3). With this knowledge in hand, we tried to detect false enhancement by evaluating pre-

and postcontrast MT images together in our study (Figure 3).

Quantitative MT studies (MT ratio, MT histogram curve, and MT properties of normal white matter) in recent years have contributed to increasing the importance and usage of the technique, in particular, by revealing important data about the heterogeneous baseline of MS. Discrimination of edema and demyelinating areas can be made by calculating MT ratios of the lesions in MS (10, 14). Petrella et al. showed in a study that MT ratios of homogenous enhancing lesions are higher than rim enhancing or nonenhancing plaques (15). Low MT ratios of nonenhancing or rim enhancing plaques probably change depending on the degree of myelin loss. In the same study, MT ratios in the center of rim enhancing lesions were decreasing due to myelin loss and were higher in the periphery of the lesion due to inflammation; this finding proved that MT ratios are important in understanding the pathological baseline of MS lesions (15). Postmortem studies in MS plaques determined that MT ratios in plaque areas decrease due to demyelination and axonal loss, but increase due to late remyelination (16).

MT ratios detected in normal white matter areas of MS patients provide important quantitative data about tissue damage, which is useful in enlightening the complex pathological process of the disease. In comparison with healthy control groups, MT ratios in plaque areas and normal white matter significantly decrease in MS (17). Rovaris et al. calculated the reduction of MT ratios in normal white matter and their results were 4.9% in secondarily progressive MS patients, 3% in overall relapsing-remitting MS patients, 2.7% in early relapsing-remitting MS patients, and 2.5% in benign MS patients, in comparison with healthy control patients. It has been demonstrated that in all MS types, and especially in secondarily progressive MS patients, there are widespread abnormalities

in not only plaque areas but normal white matter which the disease affects as well (14). In this same study, a correlation between the mean reduction of MT ratios in normal white matter and T2 lesion load, and the expanded disability status scale value was demonstrated (14). Guo et al. showed that MT ratios in normal white matter areas adjacent to MS plaques are higher than other normal white matter areas, and are lower than plaque areas (18). This is an important finding proving that myelin has been damaged in MS plaques and white matter areas adjacent to the plaques.

In conclusion, T1W MT examinations in MS yielded more reliable results in following up the treatment and the changes in the development of the disease. They also offered a more effective evaluation of the acute plaques, which caused clinical findings. For this reason, it would be more appropriate to obtain postcontrast T1W SE examinations with MT technique in imaging of active lesions in demyelinating diseases, especially MS, that cause pathological findings in white matter. Quantitative MT studies in recent years increased the importance and usage of the technique, in particular, by revealing important data about the heterogeneous baseline of MS.

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