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Imaging of active multiple sclerosis plaques: efficiency of contrast-enhanced magnetization transfer subtraction technique

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PURPOSE
T1-weighted (T1W) magnetic resonance images with magnetization transfer (MT) are widely used in the evaluation of multiple sclerosis (MS) plaques. We aimed to evaluate the contribution of the subtraction technique with MT in the detection of acute MS plaques.

MATERIALS AND METHODS
Sixty-four patients during an MS attack were enrolled in the study. Axial T1W spin echo (SE) with MT, axial-sagittal T2W fast SE, axial FLAIR and postcontrast axial T1W SE magnetic resonance imaging sequence with MT were acquired from all patients. The subtraction (postcontrast–precontrast) images were obtained on the workstation. FLAIR and T2W images were used as reference for plaque imaging. Contrast material enhanced plaques were considered as acute plaques. Qualitatively, both subtracted and contrast-enhanced with MT images were evaluated visually. Quantitatively, signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) were calculated.

RESULTS
A total of 464 plaques were detected on T2W and FLAIR images. Thirty-five acute plaques were detected on both postcontrast MT and subtracted images. Additionally, 66 acute plaques were only detected on subtracted images visually. CNR and SNR values of acute MS plaques were significantly higher on subtracted MT images than on postcontrast MT images ($P < 0.001$).

CONCLUSION
The subtraction technique seems to facilitate the detection of acute MS plaques by intensifying the visibility of poorly enhanced plaques without use of high dose contrast medium. We suggest the use of subtraction technique in routine imaging work-up of MS patients with acute attacks.

Key words: • *magnetic resonance imaging* • *magnetization transfer contrast imaging* • *multiple sclerosis*

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Multiple sclerosis (MS) is a disabling chronic demyelinating disease of young adults (1). Patients may experience relapses either during the relapsing-remitting or secondary progressive or primary progressive MS. Relapses represent new or ongoing disease activity within the central nervous system (2). Complementary to clinical assessment, magnetic resonance imaging (MRI) sensitively demonstrates the spatial and temporal dissemination of demyelinating plaques in the brain and spinal cord (3–5). It has been a useful tool for the diagnosis and assessment of treatment in MS patients (4–7).

Conventional MRI techniques such as T2-weighted (T2W) and gadolinium-enhanced T1W MRI sequences can detect MS plaques and help quantitative assessment of inflammatory activity and lesion load (3–5, 8, 9). Contrast enhancement may change with respect to both dosing of contrast material and the time between contrast injection and postcontrast image acquisition (8, 9). Late phase imaging (postcontrast images taken 15–30 min. after contrast material injection), triple dosing (0.3 mmol/kg), examination with 3 mm slices without gap, or magnetization transfer (MT) technique may improve the conspicuity of acute plaques (8–11). Late phase imaging and triple dosing increase the cost and may cause false positive results in regions with small vessels and flow artifacts (3–5, 9). Magnetization transfer (MT) technique which has increased sensitivity in the detection of MS plaques has roles in identifying the earliest stage of MS lesion genesis, edema and demyelination (12, 13). It is sensitive in assessment of the structural changes occurring in the normal appearing white- and cortical gray-matter in MS patients (12–14). Also, MT technique suppresses background signal and accentuates contrast enhancement of acute MS plaques (13–15). This study focuses on this last role of the MT technique.

An acute plaque which is buried within the white matter and invisible on T1W images may be detected with a MT pulse. T1W imaging with MT technique is not only superior in detection of the plaques but it also causes relative hyperintensity of plaques that actually do not enhance with gadolinium chelates (pseudoenhancement) (3–5, 15). If postcontrast T1W images with MT are taken into consideration alone, false positive results may occur. To overcome this problem, subtraction technique may be used (3, 15). MT pulse decreases signal-to-noise ratio (SNR) of the white matter causing an increase in the contrast-to-noise ratio (CNR) of the acute plaque. While SNR determines detection of the plaque, CNR determines discrimination of the plaque from the white matter. For a small plaque to be detectable its CNR must be high (7, 14). The brain parenchyma is seen more hypointense with subtraction technique (postcontrast T1W – precontrast T1W images) so the CNRs of contrast enhancing (hyperintense) acute plaques are expected to be higher than usual. If this were the case, there would be no need for the additional contrast material, late phase imaging, and thin slices without gap.

In the present study, we aimed to compare the diagnostic values of T1W precontrast with MT, postcontrast with MT and subtraction images with MT quantitatively in detecting plaques during a relapse, and the contribution of the subtraction MT technique in the detection of acute MS plaques.

Materials and methods

Subjects

A total of 64 (39 female, 25 male) patients being followed-up for the diagnosis of relapsing-remitting MS based on McDonald's criteria in the out-patient neurology clinic of our university medical faculty between December 2006 and October 2007 with the complaint of new onset or worsening of signs and symptoms were included in the study. They were aged between 20–56 years (mean, 32 years) with a disease duration of 2–18 years (mean, 7.6 years) and the Expanded Disability Status Scale (EDSS) of 1.0–6.0 (mean, 2.5) Their clinical status, neurological examinations and physical disability were assessed by an experienced neurologist blind to the MRI findings using EDSS within one week of MRI acquisition (16). Neurological defects lasting a minimum of 24 hours were accepted to represent an acute attack. Symptoms resulting from infection, which increases body temperature, were considered to be "false attacks" (1). 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 MRI examinations.

None of the patients with MS had other major clinical illnesses, were aged less than 20 or more than 60 years, had a history of corticosteroid use within 4 weeks preceding MRI, or a history of substance abuse. Informed consent was obtained from all participants, and the university ethics committee approved the study protocol. The patients were asked to stay immobile during the whole MRI examination to obtain good subtracted images.

MRI and analysis

All MR examinations were performed in a 1.5 T MRI device (Magnetom Vision Plus, Siemens, Erlangen, Germany) with a standard head coil according to the following MR imaging protocol: sagittal and transverse T2W fast spin-echo (FSE) (TR/TE, 5400/99 ms), axial fluid attenuated inversion recovery (FLAIR) (TR/TE/TI, 8400/114/2150 ms), axial T1W spin echo (SE) sequences with MT (TR/TE, 550/18 ms). A field of view (FOV) of 24 cm, matrix of 256×256, slice thickness of 5 mm, slice gap of 1 mm, and 2 excitations were obtained. The same T1W SE sequence with MT was performed after injection of 0.1 mmol/kg paramagnetic contrast material (gadolinium-DTPA, Magnevist, Schering, Germany). Postcontrast T1W images were obtained 5 min. after the contrast injection. Total examination duration for all the sequences was approximately 20 min. In order to prevent patient movement within the magnet while administering the contrast agent, contrast material was injected through a long-line venous access. Pre- and postcontrast images were co-registered to verify that the patients did not move between the two acquisitions.

Subtracted MT images obtained from the workstation were evaluated in terms of presence of contrast enhancement by two experienced neuroradiologists with consensus. The series of subtraction images were obtained using the software of our MR unit. Five patients were excluded due to patient motion resulting in inadequate subtracted images. A consensus about the presence of real enhancement, pseudoenhancement, vascular structure, or artifact was reached upon evaluation of all digital images. To prevent pseudoenhancement phenomenon, precontrast and postcontrast images were evaluated together with the subtracted images. The signal of a plaque was measured by a circular ROI placed on the acute plaque without extending over the edges of the plaque (S_{plaque}). The measurement from normal white matter located at the same location but contralateral to the acute plaque was performed ($S_{parenchyma}$). Values of S_{plaque} and $S_{parenchyma}$ were divided by the noise present on the images (noise) of the space outside the cranium free from artifacts in order to obtain SNR_{plaque} ($S_{plaque/noise}$) and $SNR_{parenchyma}$ ($S_{parenchyma/noise}$). Subtraction of SNR ratio of contralateral hemisphere parenchyma from SNR ratio of acute plaque gave CNR ratio of the plaque ($CNR_{plaque} = SNR_{plaque} - SNR_{parenchyma}$). SNR and CNR ratios of the acute plaques on the precontrast, postcontrast and subtracted images were calculated. For statistical analysis, ANOVA test was used. Statistical significance was set to P values lower than 0.05.

Results

A total of 464 acute or chronic MS plaques in different parts of the brain were visualized on T2W FSE and FLAIR images of 64 MS patients. Locations of plaques are shown in Table.

All of 35 acute plaques found on the postcontrast T1W SE with MT images were also detected on the subtracted images (Fig. 1). The subtraction technique increased the visual conspicuity of the acute plaques with contrast enhancement in all patients. Moreover, 66 acute plaques that went undetected on the postcontrast T1W with MT SE images were visible on the subtracted images (Fig. 2). The mean values of CNR ratios were measured as 6.6 ± 7.8, 5.1 ± 3.6 as 12.1 ± 10.8 on the precontrast T1W images with MT, on the postcontrast T1W images with MT, and on the subtracted images, respectively. The CNR ratios of plaques detected on the subtracted images were significantly higher than

Table. Locations of multiple sclerosis plaques found on T2W and FLAIR MR images

Location of plaques	Number of plaques
Deep white matter (supraventricular)	156
Deep white matter (periventricular)	148
Subcortical U-fiber level	64
Corticosubcortical junction	56
Basal nuclei	32
Pons	4
Cerebellum	4

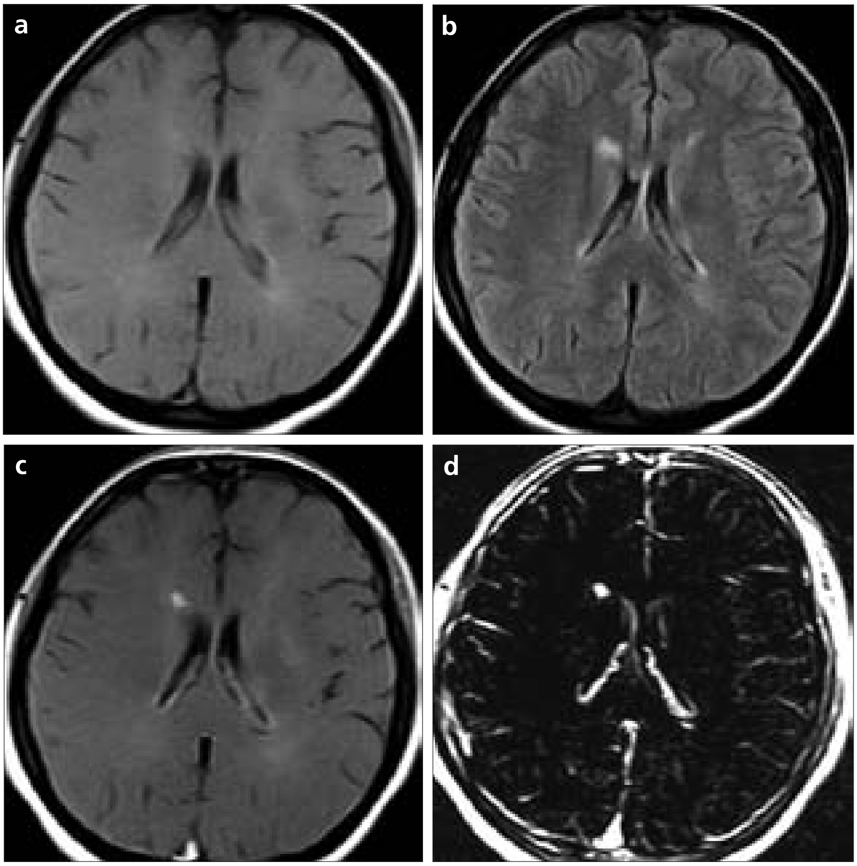

Figure 1. a–d. T1W with MT **(a)**, FLAIR **(b)**, postcontrast T1W with MT **(c)** and subtracted **(d)** MR images. The contrast-enhancing plaque in the right frontal lobe is visualized more clearly on the subtracted image.

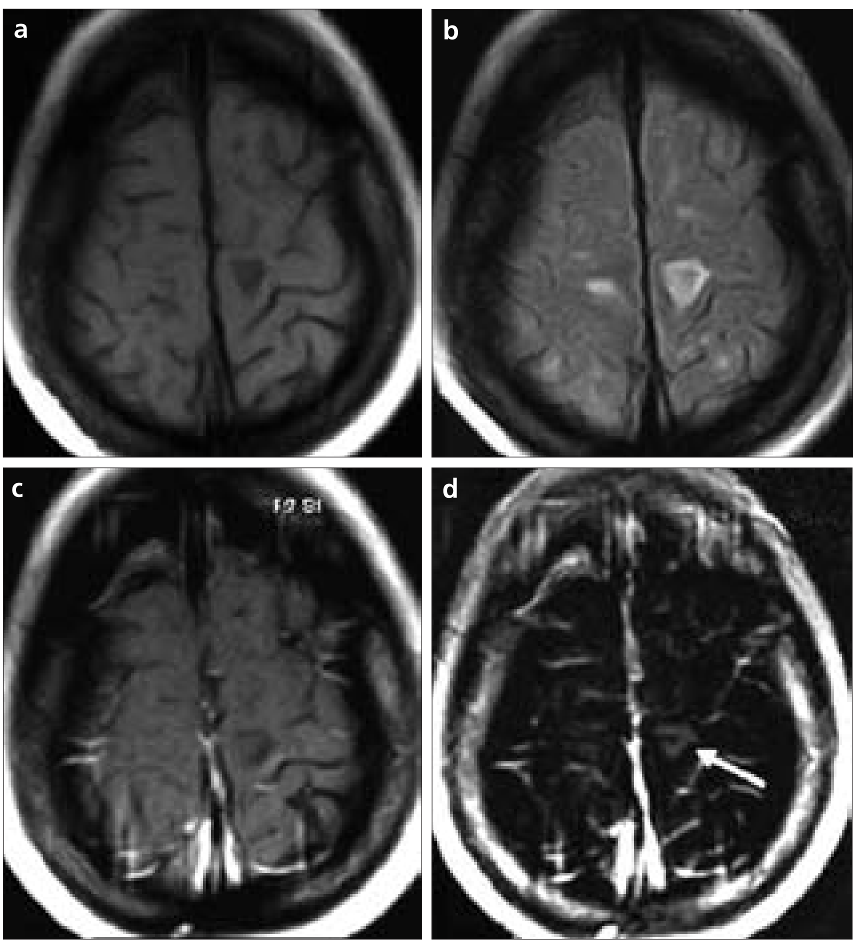

Figure 2. a–d. T1W with MT **(a)**, FLAIR **(b)**, postcontrast T1W with MT **(c)** and subtracted **(d)** MR images. Contrast enhancement of the plaque in the left cerebral hemisphere that was invisible on the postcontrast image is easily seen on the subtracted image **(***arrow,* **d)**.

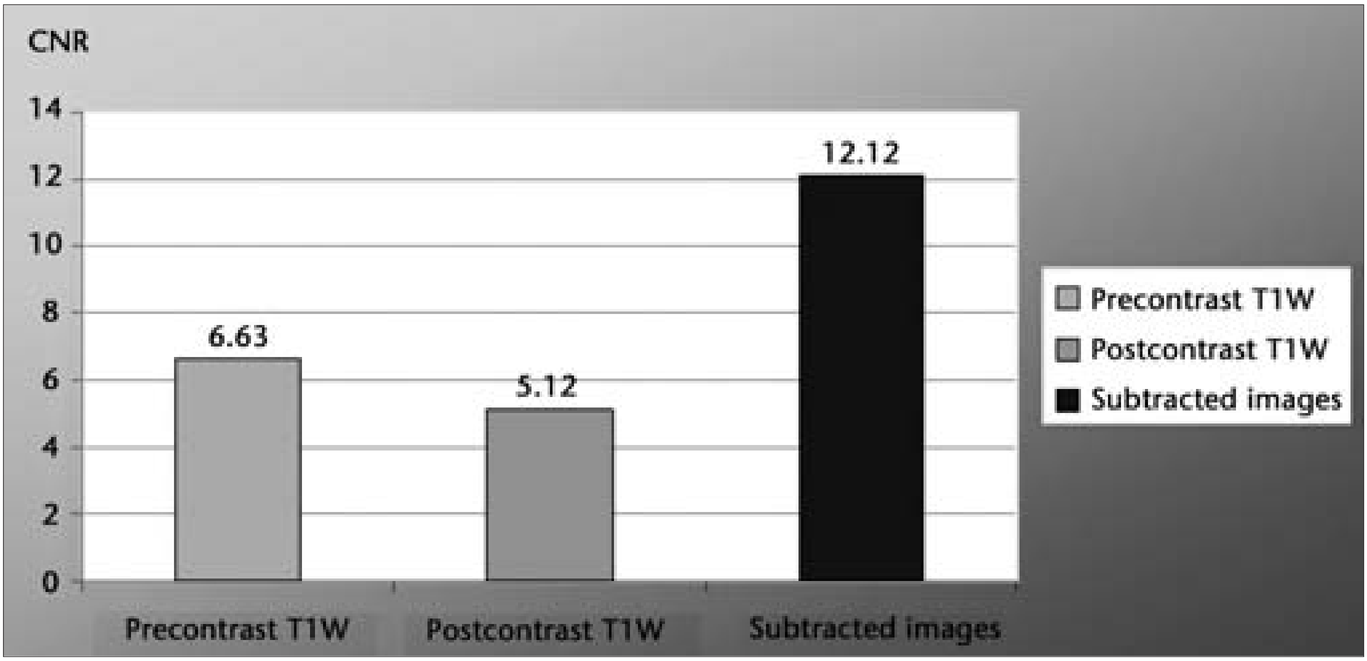

Figure 3. Contrast-to-noise ratios (CNR) of acute plaques on precontrast T1W with MT, post-contrast T1W with MT and subtracted images (ANOVA test, $P < 0.001$).

the ones detected on the precontrast or the postcontrast T1W with MT images, as shown in Fig. 3 ($P < 0.001$).

Discussion

Both acute and chronic plaques can be found on brain MRI varying according to the stage of MS, which is the most important debilitating disease among young adults (1–3). The treatment strategy changes along with the stage of the disease; therefore discrimination of the plaques with MRI is very important. MRI is one of the most objective tools for the diagnosis of the disease and the efficacy of its treatment (12, 13). MS plaques, oval shaped and multiple, are generally located in a periventricular distribution perpendicular to the lateral ventricle. The increased water content within the plaques makes them appear hyperintense on T2W and FLAIR images but hypo-/isointense on T1W images. Contrast enhancement of the acute plaques generally lasts 2–8 weeks but this duration may be even longer than 6 months (6). Acute plaques show generally ring-shaped or homogenous contrast enhancement due to the blood-brain barrier destruction (3–7, 15, 17, 18). Contrast enhancement may change according to both dosing of the contrast material and the time between the contrast injection and the postcontrast image acquisition (8, 9, 15). Late phase imaging (postcontrast images taken 15–30 minutes after contrast material injection), triple dosing (0.3 mmol/kg), examination with 3 mm slices without gap, or MT technique may improve the observation of acute plaques (8–11). Late phase imaging and triple dosing increase the cost and may cause false positive results in regions with small vessels and flow artifacts (3, 15).

MT technique is an easy, relatively new, cost-effective technique which does not increase examination duration. During the MT technique, protons bound in the brain tissue become saturated by the use of an additional off-resonance prepulse and they transfer their magnetization to free protons (3, 13, 15). This normally decreases the signal from the brain parenchyma. Signals from the acute plaques increase due to demyelination and increased edema; therefore MT images improve plaque detection (3–5, 15, 19). Evaluation of the pathological background of the plaques and discrimination between the demyelinated and edematous plaques can be made. MT technique was introduced to differentiate edema from demyelination (20, 21). We acquired neither T1W images without MT nor subtraction images without MT. One of the reasons for this was that we did not want to prolong the MR acquisition time. The other reason was our major interest for the contribution of the subtraction MT technique in the detection of acute MS plaques.

Signal intensity of MS plaques increases when compared to normal-appearing white matter on T1W images with MT pulse. If the postcontast T1W images with MT are evaluated alone, one may mistakenly consider that plaque has contrast enhancement (pseudoenhancement) (3, 15). The postcontrast and precontrast MT images must be evaluated together to avoid false positivity (8). Our study results confirmed that the subtraction technique fully prevented pseudoenhancement phenomenon (Fig. 4). The CNR ratios of acute plaques on precontrast images were significantly higher than the ones on postcontrast images ($P < 0.001$). The decrease in CNR ratios of acute plaques on postcontrast images may be attributed to the gadolinium-type contrast material decreasing T1 duration and increasing the signal from normal-appearing brain parenchyma.

Image subtraction is a postprocessing technique that is widely used in MRI to improve the visibility of contrast enhancement in applications such as sacroiliac joint imaging, abdominal imaging, and contrast-enhanced MR

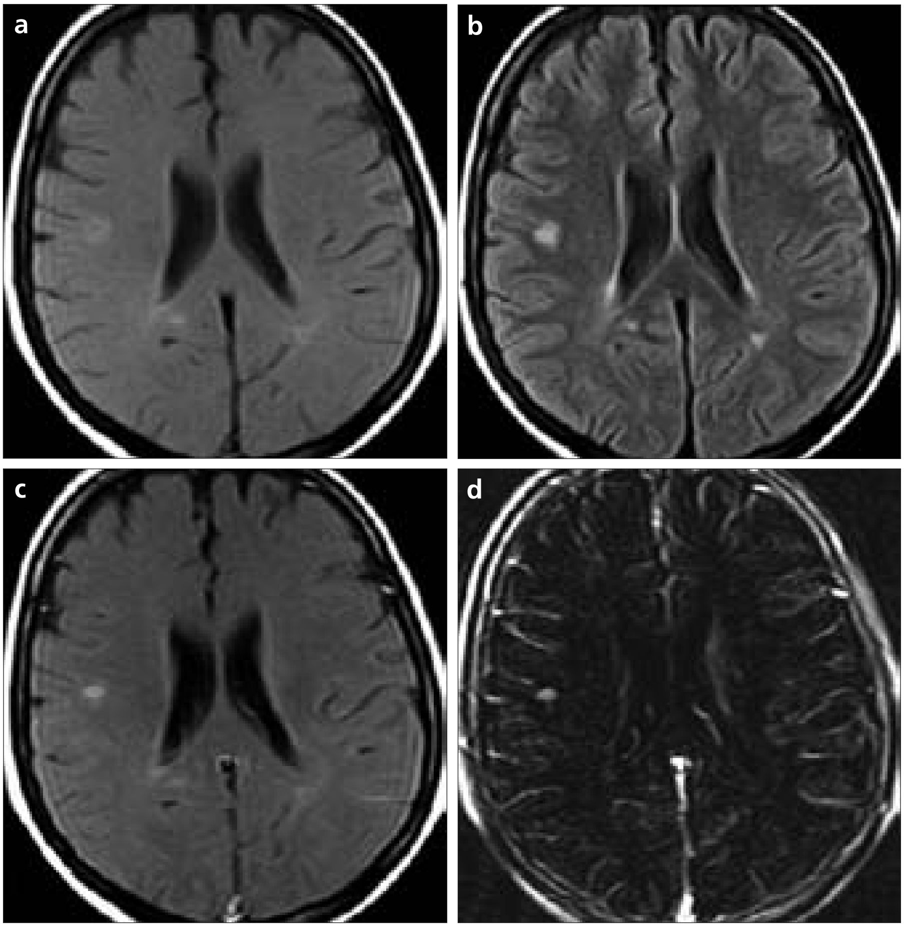

Figure 4. a–d. T1W with MT **(a)**, FLAIR **(b)**, postcontrast T1W with MT **(c)** and subtracted **(d)** MR images. The acute plaque with contrast enhancement in the right deep white matter on the postcontrast image can be seen more definitely on the subtracted image. Moreover, the plaque in the left cerebral hemisphere on T1 and FLAIR images does not show contrast enhancement on the subtracted image (pseudoenhancement phenomenon).

angiography (22, 23). There are a few publications about the value of the subtraction technique in MS (3, 15). Sardanelli et al. evaluated the value of precontrast, postcontrast and subtracted images with and without MT in 10 MS patients in detecting enhancing brain MR lesions (15). They showed that the subtracted images increased the sensitivity without MT and could be used to correct the pseudoenhancement that impairs postcontrast images with MT. While the subtracted images without MT detected more enhancing lesions, the subtracted images with MT did not. While the subtracted images were being evaluated, the pre- and postcontast images were not taken into consideration in that study so the sensitivity and the specificity of the subtracted images were relatively low. But in our study, as stated in other studies, decision about contrast enhancement was made after the evaluation of the pre- and postcontrast images along with the subtracted images with MT (3, 8, 10, 11). Gavra et al. found 52 enhancing lesions on postcontrast T1W images without MT in 31 MS patients (3). Postcontrast T1W images with MT allowed the detection of an extra 13 enhancing lesions (7 patients) compared with postcontrast T1W images without MT (3). The subtraction images without MT allowed the detection of an extra 10 enhancing lesions compared with postcontrast T1W images without MT; the subtraction MT images were not taken into consideration in this study (3).

The number of patients and image groups being compared in our study were different from similar studies. Both of two similar studies were done in a limited number of patients and the acute plaques were defined according to subjective criteria (3, 15). These studies did not evaluate CNR ratios of acute MS plaques unlike our study. Also, pre- and postcontrast images with MT were not compared with subtracted images in these studies. By using the subtraction MT method, we detected 66 extra acute plaques invisible on the postcontrast MT images. The CNR values of the acute plaques on the subtracted images were significantly higher than the ones on the pre- and postcontrast MT images ($P < 0.001$). High CNR values on the subtraction images provide easy detection of the acute plaques.

The most important limitation of the subtraction technique is its high susceptibility to motion. Venous structures within the brain parenchyma seen on the subtracted images may mimic contrast-enhancing MS plaques. Evaluation of the lesions found on the subtracted images in correlation with other images in the workstation and tracing the course of the vascular structures will help to overcome this problem. When an acute plaque is detected on the subtracted images, presence of its counterpart on T1W and T2W images should be checked.

In conclusion, the combination of MT, contrast material administration, and subtraction images is synergistic. Also, image subtraction technique increases detection of acute plaque both qualitatively and quantitatively. The subtraction technique is a fast, basic, and cost-effective method which does not increase examination duration and prevents the pseudoenhancement phenomenon on the postcontrast images with MT. We recommend routine use of the subtraction method with MT in detection of the acute plaques in MS patients.

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