MAJOR PAPER

Detection of Active Plaques in Multiple Sclerosis using Susceptibility-weighted Imaging: Comparison with Gadolinium-enhanced MR Imaging

Masako SUZUKI¹, Kohsuke KUDO^{2*}, Makoto SASAKI², Satoshi TAKAHASHI¹,
Jyunko TAKAHASHI¹, Noriyuki FUJIMA³, Ikuko UWANO², Hisashi YONEZAWA¹,
Masako KUDO¹, Hikoaki FUKAURA¹, Naoki ISHIZUKA¹, and Yasuo TERAYAMA¹

¹Department of Neurology and ²Advanced Medical Research Center, Iwate Medical University
19-1 Uchimaru, Morioka 020-8505, Japan

³Department of Radiology, Hokkaido University Graduate School of Medicine

(Received January 7, 2011; Accepted March 30, 2011)

Purpose: Susceptibility-weighted (SW) imaging is a magnetic resonance (MR) imaging technique reported effective in visualizing multiple sclerosis (MS) plaques, but its capacity to distinguish active plaques remains unclear. We evaluated active plaque detection by SW compared with contrast-enhanced MR imaging.

Methods: We prospectively examined 11 patients using a 3-tesla scanner. Two neuroradiologists independently evaluated signal changes of plaques and accompanying low signal rims in 74 plaques on various SW images (magnitude, phase, and minimum intensity projection [minIP]), and on contrast-enhanced T₁-weighted images (T₁WI). We correlated signal alterations on various SW images and contrast enhancement on T₁WI using Fisher's exact test and calculated sensitivity and specificity for predicting gadolinium enhancement.

Results: Only changes in plaque signal on SW magnitude images correlated significantly with contrast enhancement of the plaques ($P=0.008$), and high signal intensity had 0.556 sensitivity and 0.787 specificity for predicting contrast-enhanced plaques. Furthermore, plaques with rims of low signal showed sensitivity of 0.296 and specificity of 0.957.

Conclusions: Susceptibility-weighted magnitude, but not phase or minIP, images can predict MS plaques with contrast enhancement with high specificity.

Keywords: *contrast enhancement, magnitude image, multiple sclerosis, phase image, susceptibility-weighted imaging*

Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system with elusive origins that progresses mainly by autoimmune mechanisms,¹ and most patients experience multiple episodes of relapse and remission. Accurate diagnosis and monitoring of disease activity by magnetic resonance (MR) imaging are crucial for prompt and appropriate management to reduce relapse occurrence and slow disease progression to disability.^{2,3}

Structural MR images, such as T₂-weighted (T₂WI) and fluid-attenuated inversion recovery (FLAIR) images, demonstrate similar signal intensity and configuration of active and inactive MS

plaques, so detecting new plaques requires repetitive examination and image comparison. Because actual demyelination activity in plaque cannot be determined using these images, gadolinium (Gd)-enhanced T₁-weighted images (T₁WI) have been widely used to reveal abnormal enhancement of newly developed or relapsed active plaques.⁴⁻⁷ Nevertheless, contrast-enhanced MR imaging cannot be applied in patients with renal dysfunction or history of allergic reactions.⁸

Susceptibility-weighted imaging (SWI) has been developed as a novel MR imaging technique to visualize venous structure, iron deposition, and hemorrhage⁹⁻¹¹ without the use of contrast agents. Several recent studies applying SWI to MS¹²⁻¹⁴ have reported that minimum intensity projection (minIP) SWI and/or its source images before post-processing (i.e., SW magnitude and phase images) can

*Corresponding author, Phone: +81-19-651-5111, Fax: +81-19-654-9860, E-mail: kokudo@iwate-med.ac.jp

detect MS plaques with greater sensitivity than structural MR imaging and can visualize various signal patterns not previously recognized within the plaques. However, it is not clear which findings on various SW images correspond to abnormal enhancement on T₁WI and readily reflect plaque activity. Therefore, we attempted to identify imaging findings that predict plaque activity without contrast media by analyzing signal patterns of plaque on various SW images, including SW magnitude, phase, and minIP images, and correlating these with findings from contrast-enhanced T₁WI.

Materials and Methods

Patients

Between July 1st, 2009 and February 28th, 2010, we prospectively recruited 45 consecutive patients with relapsing-remitting type MS. Inclusion criteria were age 15 to 60 years, onset of less than 10 years, and presence of plaque(s) in the supratentorial region on previous MR imaging. Exclusion criteria were neuromyelitis optica, renal dysfunction, and history of allergic reactions to Gd agents. Among the 45 patients, 11 (8 women, 3 men) met study criteria. Mean age was 32 years (range, 19 to 47 years) and mean disease duration was 4.6 years (range, 0.5 to 8.5 years). All patients were diagnosed with relapsing-remitting type MS according to the 2005 McDonald criteria for MS diagnosis.¹⁵ At study entry, 6 patients were in relapse, and five were in remission. None had evidence or prior diagnosis of neoplasms, cerebrovascular diseases, or other neurological disorders. The local institutional review board approved the study protocol, and all patients provided written informed consent.

MR imaging examination

Imaging examinations were conducted using a 3-tesla MR scanner (Signa HDx; GE Healthcare, Milwaukee, WI, USA) with a standard quadrature detection (QD) head coil. For SWI, 3-dimensional (3D) spoiled gradient-echo (SPGR) images were obtained using parameters: repetition time (TR), 48 ms; echo time (TE), 30 ms; field of view (FOV), 240 mm; acquisition matrix size, 512 × 256; slice thickness, 1.5 mm; number of slices, 90; flip angle (FA), 18°; and acquisition time, 16 min 54 s. After signal acquisition, we reconstructed SW magnitude images in addition to real and imaginary images on the console. We used Perfusion Mismatch Analyzer (PMA) Ver. 3.3.0.0 freeware software to generate unwrapped SW phase and minIP images using previously described methods.^{16,17} Briefly, after unwrapping background phase shifts by applying a

high-pass filter (kernel size, 64 × 64), we obtained unwrapped SW phase and phase mask images. The phase mask images were multiplied 4 times followed by multiplication on the SW magnitude images. We then used a minIP technique with 6-mm slice thickness to generate minIP SWIs. These post-processing parameters were routinely used in our institute.

We obtained T₂WI and T₁WI before and after administration of Gd contrast (0.1 mmol/kg gadoteridol; Bracco-Eisai Co., Tokyo, Japan). For T₂WI, we used 2-dimensional (2D) fast spin-echo (FSE) technique (TR, 4000 ms; TE, 92 ms; FOV, 240 mm; acquisition matrix size, 512 × 256; slice thickness, 4 mm with interslice gaps of 0.5 mm; number of slices, 24; and acquisition time, 7 min), and for pre- and postcontrast T₁WI, we used 3D SPGR technique (TR, 11.8 ms; TE, 3.84 ms; FOV, 240 mm; acquisition matrix size, 512 × 256; slice thickness, 1.5 mm; number of slices, 90; FA, 15°; and acquisition time, 4 min 46 s).

Visual interpretation of plaque findings

From T₂WIs, one neurologist (S. M.) selected for visual assessment lesions with ovoid hyperintensity in the supratentorial regions that suggested MS plaques. A total of 74 plaques was selected. Two board-certified neuroradiologists (K. K. and N. F.) independently evaluated the intensity of plaques (i.e., low, iso-, or high intensity) compared with surrounding normal white matter and accompanying rim hypointensity¹² on SW magnitude, phase, and minIP images. T₂WI was used as a reference to identify plaque size and location.

To calculate intraobserver agreement, we conducted 2 reading sessions one week apart in which plaques were randomly presented. In a third session, each reader determined a final evaluation for plaques for which there was a discrepancy between the first and second sessions. When final plaque assessments varied between readers, consensus was sought. One month later, the same readers evaluated the signal intensity of the plaques on pre- and postcontrast T₁WIs to describe the presence of contrast enhancement and its pattern, i.e., intraplaque or ring-like enhancement. Discrepancies between sessions and readers were treated in the same manner as described above.

Statistical analysis

We used Fisher's exact test to determine whether the signal intensity of plaques, hypointensity of rims, and any combination of these on SW magnitude, phase, or minIP images correlated with plaque enhancement on postcontrast T₁WI. We

calculated sensitivities and specificities after dividing high, iso-, and low signal intensities into 2 categories. For example, to calculate sensitivity of high signal plaques, we divided signal intensities into one category with high intensity and a second with iso or low intensity. We examined intra- and interobserver agreements using kappa statistics. All statistical tests were performed using SPSS Version 18 statistical software (SPSS Inc., Chicago, IL, USA). An alpha level of 0.01 denoted statistical significance.

Results

We evaluated 74 plaques, all of which showed low signal intensity on precontrast T_1 WI and 27 (36.5%) of which showed contrast enhancement effects on postcontrast T_1 WI. Among various signal alterations of MS plaques on SW magnitude, phase, and minIP images, only those on SW magnitude images correlated significantly with Gd enhan-

cement ($P=0.008$, Fisher's exact test). The rate of contrast enhancement increased as signal intensity increased—11.1% in plaques with low intensity, 27.5% in isointense plaques, and 60.0% in plaques with high intensity (Fig. 1a). When high intensity on SW magnitude images was used to predict contrast enhancement, sensitivity was 0.556 and specificity, 0.787. In contrast, enhancement was not significantly related to signal alterations on SW phase ($P=0.354$) or minIP ($P=0.546$) images or accompanying hypointense rim on SW magnitude ($P=0.075$), phase ($P=0.197$), or minIP ($P=0.240$) images (Fig. 1b–f).

Among combined findings of high intensity on SW magnitude images with signal changes on other images or presence of low intensity rim signal on any images, Gd enhancement correlated significantly only in combinations with low signal rim on SW magnitude and minIP images ($P=0.004$ for both) (Table). Sensitivity was 0.296 and specificity, 0.957, for both combinations.

Fig. 1. Relationship between signal changes on various susceptibility-weighted (SW) images and enhancement effects on postcontrast T_1 -weighted images of demyelinating lesions in patients with multiple sclerosis. Upper row (a–c), signal intensity of the plaque; lower row (d–f), accompanying hypointense rim; black area in bars, plaques with contrast enhancement; P -values, Fisher's exact test. Alterations in plaque signal correlated significantly with contrast enhancement, i.e., increased intensity of plaque signal resulted in increased rate of contrast enhancement only on SW magnitude images (a). In contrast, no significant relationships were observed between signal alterations of plaques on SW phase (b) or minIP (c) images and enhancement effects. No significant relationship was observed between accompanying hypointense rim on any images and Gd enhancement (d–f).

Table. Prediction of contrast enhancement effects of demyelinating plaques using combined imaging findings on susceptibility-weighted and source images

Images	Findings	n	<i>P</i> -Value*	Sensitivity	Specificity
SW magnitude	high intensity	25	0.008	0.556	0.787
+ SW magnitude	rim +	10	0.004	0.296	0.957
	rim –	15	0.382	0.259	0.830
+ SW phase	high intensity	7	0.701	0.111	0.915
	isointensity	13	0.057	0.296	0.894
	low intensity	5	0.056	0.148	0.979
	rim +	15	0.069	0.333	0.872
	rim –	10	0.156	0.222	0.915
+ minIP SWI	high intensity	3	0.550	0.074	0.979
	isointensity	18	0.023	0.407	0.851
	low intensity	4	0.620	0.074	0.957
	rim +	10	0.004	0.296	0.957
	rim –	15	0.382	0.259	0.830

* Fisher's exact test; minIP, minimum intensity projection; SWI, susceptibility-weighted images/imaging. + and – indicate presence and absence of a rim, respectively.

With regard to relationship with plaque enhancement pattern on postcontrast T_1 WI, 12 plaques presented a ring-like pattern, eight of which had hypointense rim on SW magnitude images and seven, on minIP SWIs. In the other 15 plaques, which demonstrated enhancement within the plaque, signal intensity was high in 7 plaques and isointense in 8 plaques on SW magnitude images, and 6 plaques had accompanying hypointense rim on SW magnitude images and 3 plaques, on minIP SWIs. Figures 2 to 4 show typical image findings of the plaques.

Values of κ ranged from 0.508 to 0.827 for intraobserver agreement, indicating moderate agreement, and from 0.336 to 0.526 for interobserver agreement, indicating poor to moderate agreement.

Discussion

Several studies have evaluated MS plaques using minIP SWIs or SW phase images,^{12,13} but SW magnitude images have not been an area of focus. In this study, however, we found significant correlation between signal alterations of plaque on SW magnitude images, i.e., high intensity plaques with or without low signal rims, and enhanced plaques on Gd-enhanced T_1 WI, whereas signal changes on SW phase or minIP images did not correspond with enhancement. Our results indicate that magnitude images obtained by SWI technique contain information not available in SW phase or minIP images that can be used to predict active plaques with contrast enhancement with moderate sensitivity and high specificity.

There are several possible explanations why ac-

tive plaques tended to show high intensity on SW magnitude images. Because we obtained images using a 3D SPGR technique with long TE, the signal alteration depends on T_2^* as well as T_1 and T_2 , so T_1 shortening and/or T_2 prolongation may provide the signal increase of MS plaques. In general, T_1 shortening in brain lesions can occur with paramagnetic effects by methemoglobin (met-Hb), free radicals, nonheme irons such as ferritin, lipids, proteinaceous materials, hypermyelination, melanin, and minerals, such as manganese (Mn) and copper (Cu).¹⁸ Among these, the candidates that appear to account for the high intensity of active MS plaques on SW magnitude images are the free radicals produced by phagocytotic cells, such as macrophages and microglia, nonheme iron within phagocytotic cells, lipids in debris of broken-down myelin sheath, and proteinaceous materials by leakage of serum into the brain tissue.^{19–22} Although MS plaques have been reported to show high intensity on T_1 WIs,^{23,24} we had no plaques with high signal intensity on both SW magnitude and T_1 WI images. The discrepancy between SW magnitude images and T_1 WIs can be partly attributed to alterations in the T_1 contrast from longer TR in the SW magnitude images. Furthermore, the high intensity of MS plaques on SW magnitude images can be partly explained by T_2 prolongation primarily resulting from vasogenic edema in the active phase. However, MS plaques, either active or inactive, usually show high signal intensity on T_2 WI and have similar T_2 values.⁵ We propose that T_2^* shortening can occur by accumulation of hemosiderins in the chronic phase and may mask high intensity by T_2

Fig. 2. Signal changes on susceptibility-weighted (SW) magnitude, phase, and minIP images of contrast-enhanced plaque of a patient with multiple sclerosis. A 20-year-old woman in relapse phase. (a) T₂-weighted image, (b) precontrast T₁-weighted image, (c) postcontrast T₁-weighted image, (d) SW magnitude image, (e) SW phase image, and (f) minimum intensity projection (minIP) SWI. A round lesion not seen on previous examination (2 months prior, not shown) is depicted with high intensity on T₂-weighted image and low intensity on T₁-weighted image (a, b, arrows). The lesion shows homogeneous enhancement on postcontrast T₁-weighted image (c, arrow), suggesting an active demyelinating plaque. On the SW magnitude image, the plaque shows high intensity compared to the adjacent normal white matter (d, arrow) but isointensity on SW phase and minIP images (e, f, arrows). The hypointense rim around the plaque is not identified on any images.

prolongation. Further comparative studies with pathological findings are needed to investigate the mechanisms of signal alterations in active and inactive plaques on various SW images.

In this study, the coexistence of low intensity rim on the same SW magnitude or minIP SW images improved the specificity of plaques with high intensity on SW magnitude images to predict active plaques. Previous pathological studies revealed accumulation of phagocytic cells laden with ferritin or hemosiderin mainly at the plaque border,^{22,25} so we attribute signal attenuation at the rim of the MS plaque to T₂ and/or T₂* shortening from deposition of ferritin and/or hemosiderin. Low intensity rim was also detected on minIP SWIs, as previously reported,¹² and we found that it correlated with enhanced plaques.

The SWI technique has recently been used to assess MS, but most studies focused on findings from SW minIP or phase images. To our knowledge, no study has reported the importance of SW magnitude images. minIP SWI contains information

from SW magnitude and phase images, usually phase-weighted,^{13,16,17} so under some conditions, the countervail of the phase shift might mask the signal alteration of SW magnitude images on minIP SWIs. Thus, abnormal signal changes of plaques might be overlooked when only minIP SWIs and SW phase images are interpreted. In this study, plaques with high intensity on SW magnitude images, which were important in predicting active plaques, frequently disappeared on minIP SWIs when those on the SW phase image showed low intensity. Our results suggest that evaluation of MS plaques should include SW magnitude images in addition to minIP SWIs and SW phase images.

Although contrast enhancement on T₁WI is one criterion for active MS plaques,¹⁵ less invasive assessment of activity in MS plaques is needed clinically to be more cost effective and to evaluate patients in whom Gd agents cannot be used. We observed substantial correspondence of signal changes in plaques on SW magnitude images with enhancement effect on T₁WIs, but these changes

Fig. 3. Signal changes on susceptibility-weighted (SW) magnitude, phase, and minimum intensity projection (minIP) images of the contrast-enhanced plaque of a patient with multiple sclerosis (MS). A 26-year-old woman in remission phase. (a) T₂-weighted image, (b) precontrast T₁-weighted image, (c) postcontrast T₁-weighted image, (d) SW magnitude image, (e) SW phase image, and (f) minIP SWI. An ovoid lesion of MS plaque not seen on previous examination (3 months prior, not shown) is seen on T₂WI (a, arrow). The plaque shows low signal intensity on T₁WI (b, arrow) and ring-like enhancement on gadolinium (Gd)-enhanced T₁WI (c, arrows). On SW magnitude image, the plaque shows high signal intensity compared to normal white matter (d, arrow) with hypointense rim (arrowheads). This plaque shows markedly low signal intensity on SW phase image (e, arrow), whereas the signal of the plaque is slightly low on minIP SWI (f, arrow).

were not sufficiently sensitive to become a surrogate marker for plaque activity. Longitudinal studies with a larger population are necessary to establish advantages of SWI techniques to improve accuracy of plaque activity detection, achieve early treatment, reduce relapse frequency, and slow down disability progression in patients with MS.

This study had several limitations. First, we used the enhancement effect of the Gd contrast agent as a gold standard for active plaques, according to previous reports,²⁻⁴ but such enhancement is known to be insufficiently sensitive to active plaques²⁶ and may occur even in inactive plaques.²² Hence, we cannot confirm the true sensitivity and specificity of SW magnitude images in predicting plaque activity. Second, we did not perform quantitative evaluation by measuring the region of interest (ROI), which is considered more objective than visual evaluation, because we reasoned that visual assessment is a practical method in daily practice. However, suboptimal intra/interobserver agreement in this study suggests the need for quantitative methods to im-

prove accuracy and repeatability for assessing MS plaques using various SW images. Third, the slice thickness of T₂WIs, which we used for the reference of plaque location and size, was different from that of SWI and T₁WI, which could diminish accuracy and reproducibility during visual assessment. This issue can be resolved using a 3D FSE technique with alternating refocusing radiofrequency (RF) pulses, but this was not available in our scanner during this study. Fourth, we evaluated only ovoid lesions in the supratentorial white matter. Including infratentorial plaques could increase the number of plaques for evaluation, but susceptibility artifacts were prominent on minIP SWI, SW magnitude, and SW phase images in the brain stem and cerebellum. Neither did we include in our study plaques that did not appear on T₂WI. Some plaques are reported to show signal change only on SW phase images or minIP SWI.¹² Further studies are needed to evaluate these plaques as well as lesions in white matter that appear normal, U-fiber lesions, and cortical lesions that can occur in MS.

Fig. 4. Signal changes on susceptibility-weighted (SW) magnitude, phase, and minimum intensity projection (minIP) images of nonenhanced plaque of a patient with multiple sclerosis (MS). A 28-year-old man in remission phase. (a) T₂-weighted image, (b) precontrast T₁-weighted image, (c) postcontrast T₁-weighted image, (d) SW magnitude image, (e) SW phase image, and (f) minIP SWI. An ovoid lesion of MS plaque seen on previous examination 3 months prior is seen on T₂WI (a, arrow). The plaque shows low signal intensity on T₁WI (b, arrow), and contrast enhancement is not observed on gadolinium (Gd)-enhanced T₁WI (c, arrow). On SW magnitude, phase, and minIP images, the plaque shows low signal intensity compared to normal white matter (d, e, and f, arrows).

Conclusion

Among a variety of SW images, we found that the high signal intensity of SW magnitude images showed high specificity for and therefore can be a practical predictor of active MS plaques with contrast enhancement, whereas signal intensities of SW phase image or minIP SWI showed no significant relationship with contrast enhancement. An SW magnitude image with long echo time and high spatial resolution can be used to evaluate the activity of MS plaques.

Acknowledgements

This work was supported by a Grant-in-Aid for the Strategic Medical Science Research Center from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

This work was presented at the 2010 annual meeting of JSMRM.

References

1. Kornek B, Lassmann H. Neuropathology of multiple sclerosis-new concepts. *Brain Res Bull* 2003; 61:321–326.
2. Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. *Lancet* 2007; 370: 389–397.
3. Miller JR. The importance of early diagnosis of multiple sclerosis. *J Manag Care Pharm* 2004; 10: S4–S11.
4. Filippi M. Enhanced magnetic resonance imaging in multiple sclerosis. *Mult Scler* 2000; 6:320–326.
5. Grossman RI, Gonzalez-Scarano F, Atlas SW, Galetta S, Silberberg DH. Multiple sclerosis: gadolinium enhancement in MR imaging. *Radiology* 1986; 161:721–725.
6. Grossman RI, Braffman BH, Brorson JR, Goldberg HI, Silberberg DH, Gonzalez-Scarano F. Multiple sclerosis: serial study of gadolinium-enhanced MR imaging. *Radiology* 1988; 169:117–122.

7. Miller DH, Rudge P, Johnson G, et al. Serial gadolinium enhanced magnetic resonance imaging in multiple sclerosis. *Brain* 1988; 111(Pt. 4):927-939.
8. Bardin T, Richette P. Nephrogenic systemic fibrosis. *Curr Opin Rheumatol* 2010; 22:54-58.
9. Ge Y, Zohrabian VM, Osa EO, et al. Diminished visibility of cerebral venous vasculature in multiple sclerosis by susceptibility-weighted imaging at 3.0 Tesla. *J Magn Reson Imaging* 2009; 29:1190-1194.
10. Haacke EM, Xu Y, Cheng YC, Reichenbach JR. Susceptibility weighted imaging (SWI). *Magn Reson Med* 2004; 52:612-618.
11. Ayaz M, Boikov AS, Haacke EM, Kido DK, Kirsch WM. Imaging cerebral microbleeds using susceptibility weighted imaging: one step toward detecting vascular dementia. *J Magn Reson Imaging* 2010; 31:142-148.
12. Haacke EM, Makki M, Ge Y, et al. Characterizing iron deposition in multiple sclerosis lesions using susceptibility weighted imaging. *J Magn Reson Imaging* 2009; 29:537-544.
13. Eissa A, Lebel RM, Korzan JR, et al. Detecting lesions in multiple sclerosis at 4.7 tesla using phase susceptibility-weighting and T₂-weighting. *J Magn Reson Imaging* 2009; 30:737-742.
14. Mittal S, Wu Z, Neelavalli J, Haacke EM. Susceptibility-weighted imaging: technical aspects and clinical applications, part 2. *AJNR Am J Neuroradiol* 2009; 30:232-252.
15. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." *Ann Neurol* 2005; 58:840-846.
16. Kudo K, Sasaki M, Yamada K, et al. Differences in CT perfusion maps generated by different commercial software: quantitative analysis by using identical source data of acute stroke patients. *Radiology* 2010; 254:200-209.
17. Kudo K, Sasaki M, Ogasawara K, Terae S, Ehara S, Shirato H. Difference in tracer delay-induced effect among deconvolution algorithms in CT perfusion analysis: quantitative evaluation with digital phantoms. *Radiology* 2009; 251:241-249.
18. Quint DJ. Hyperintense disks on T₁-weighted MR images: are they important? *Radiology* 1995; 195:325-326.
19. Connor JR, Menzies SL, Burdo JR, Boyer PJ. Iron and iron management proteins in neurobiology. *Pediatr Neurol* 2001; 25:118-129.
20. Haimes AB, Zimmerman RD, Morgello S, et al. MR imaging of brain abscesses. *AJR Am J Roentgenol* 1989; 152:1073-1085.
21. Terada H, Barkovich AJ, Edwards MS, Ciricillo SM. Evolution of high-intensity basal ganglia lesions on T₁-weighted MR in neurofibromatosis type 1. *AJNR Am J Neuroradiol* 1996; 17:755-760.
22. Brück W, Bitsch A, Kolenda H, Brück Y, Stiefel M, Lassmann H. Inflammatory central nervous system demyelination: correlation of magnetic resonance imaging findings with lesion pathology. *Ann Neurol* 1997; 42:783-793.
23. Guttmann CR, Ahn SS, Hsu L, Kikinis R, Jolesz FA. The evolution of multiple sclerosis lesions on serial MR. *AJNR Am J Neuroradiol* 1995; 16:1481-1491.
24. Janardhan V, Suri S, Bakshi R. Multiple sclerosis: hyperintense lesions in the brain on nonenhanced T₁-weighted MR images evidenced as areas of T₁ shortening. *Radiology* 2007; 244:823-831.
25. Craelius W, Migdal MW, Luessenhop CP, Sugar A, Mihalakis I. Iron deposits surrounding multiple sclerosis plaques. *Arch Pathol Lab Med* 1982; 106:397-399.
26. Tas MW, Barkhol F, van Walderveen MA, Polman CH, Hommes OR, Valk J. The effect of gadolinium on the sensitivity and specificity of MR in the initial diagnosis of multiple sclerosis. *AJNR Am J Neuroradiol* 1995; 16:259-264.