

Multiple Sclerosis

What Have We Learned From Magnetic Resonance Imaging Studies?

Samia J. Khoury, MD; Howard L. Weiner, MD

We review studies that have examined the relationship between magnetic resonance imaging findings and clinical disability, postmortem observations, and cognitive dysfunction in patients with multiple sclerosis. We also review the use of magnetic resonance imaging findings as an outcome measure in clinical trials assessing the efficacy of new therapeutic agents for the treatment of multiple sclerosis. More advanced applications of magnetic resonance imaging and their use in multiple sclerosis is addressed later in the article.

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Multiple sclerosis (MS) is a progressive, degenerative disease of the central nervous system whose distinguishing feature is the development of scattered, focal lesions of the myelin sheath of the axons.¹ The disease usually strikes in the third or fourth decade of life and affects more women (60% of cases) than men (40% of cases).¹ In 1990 in the United States, about 250 000 to 300 000 cases of MS were diagnosed by physicians.²

COURSE OF MS

The clinical course of MS is generally marked by the appearance of new symptoms, remissions, and exacerbations over periods of years, although rare cases may progress to death within weeks to months.¹ Several patterns of MS remission-exacerbation have been identified and described. In the early relapsing-remitting pattern, periods of acute clinical symptoms lasting for days to weeks are followed by periods of recovery. Patients with early relapsing-remitting MS may be classified as having the benign MS pattern if they continue to have relapsing-remitting disease with only minimal disability after a disease duration of at least 10 years.³ Some pa-

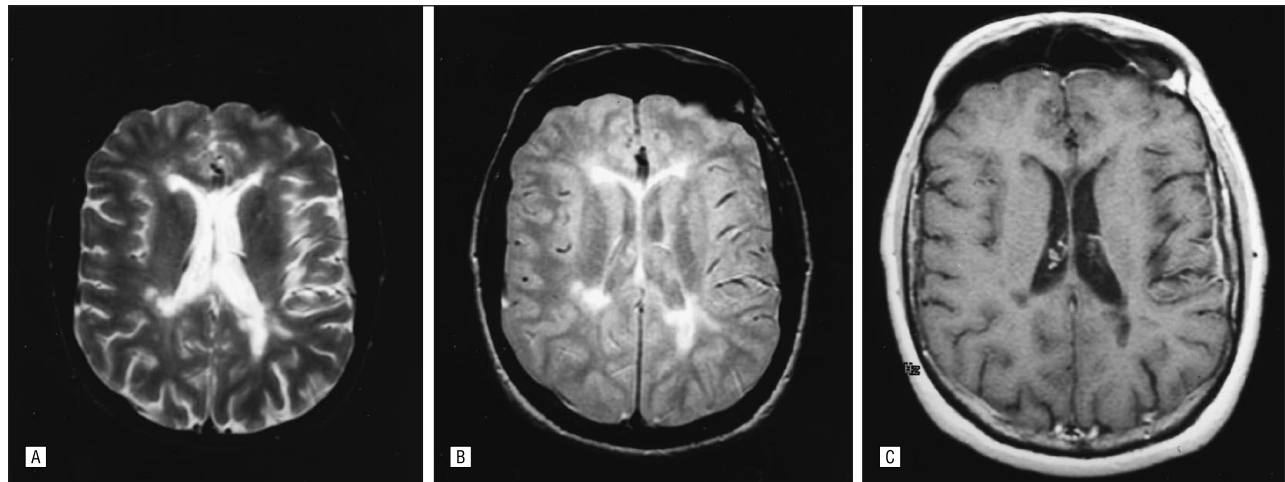
tients subsequently develop a form of MS that is marked by a progressive decline in neurological function for longer than 6 months⁴; they are said to have secondary-progressive MS.⁵ Other patients present with the primary-progressive pattern in which progressive deterioration occurs from the time of initial diagnosis.³ A course of neurological deterioration that is progressive from the outset and also is superimposed with random acute attacks is now said to be progressive-relapsing.⁵

MEASUREMENT OF DISABILITY

Several clinical rating scales have been used to assess the degree of neurological dysfunction in patients with MS and to measure treatment effectiveness.⁶ The Expanded Disability Status Scale (EDSS), developed by Kurtzke,⁷ is the most widely used method of scoring disability associated with MS. The limitations of this scale with respect to interrater and intrarater reliability as well as sensitivity have been recently reviewed by Noseworthy.⁶

The Neurologic Rating Scale, developed by Sipe and coworkers,⁸ is based on assessment of each component of the neurological examination and reflects overall neurological function. The Ambulation Index scale is a reproducible measure of lower limb disability.^{9,10}

From the Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, Mass.



A slice of magnetic resonance imaging scan of a patient with multiple sclerosis showing characteristic periventricular lesions with increased signal on T_2 -weighted (A) and proton-density (B) images. A gadolinium-enhanced magnetic resonance imaging scan did not show enhancing lesions, but some of the lesions seen on T_2 appear hypointense on T_1 (C).

MRI AND MS: AN INTRODUCTION

Magnetic resonance imaging uses a magnetic field to align all hydrogen nuclei within body tissue in the same direction. A radiofrequency pulse sequence is applied to the tissue to push the hydrogen nuclei out of alignment with their previous path. When the radiofrequency pulse ends, the hydrogen nuclei return to their original position. The amount of time it takes a hydrogen nucleus to return to its original direction within the magnetic field is the T_1 relaxation time.¹¹ The T_2 relaxation time is the time it takes for the hydrogen nucleus to lose the energy that keeps it aligned within the original magnetic field. T_2 is always shorter than T_1 .¹¹

IMAGE CHARACTERISTICS

The brightness and other characteristics of the image produced by the changes in the magnetic field in magnetic resonance depend both on the concentration of the hydrogen nuclei in the tissue (called the proton density or spin density) and the weight given to the T_1 and T_2 components of the image, which is determined by the radiofrequency pulse sequence.¹¹ On T_1 -weighted images, tissues with a short T_1 appear brighter than those with a long T_1 , while on T_2 -weighted images, tissues with a long T_2 appear brighter than those with a short T_2 .¹¹ Proton-density images (with characteris-

tics between those of T_1 - and T_2 -weighted images) show a sharp contrast between cerebrospinal fluid and brain tissue (**Figure**).¹²

When a radiofrequency pulse sequence with a long time between pulses (2000-3000 milliseconds) and 2 echos (at 20-30 milliseconds and 70-90 milliseconds) is used, the first echo produces a proton-density image that contrasts MS lesions (hyperintense) with the cerebrospinal fluid (hypointense), while the second echo produces an image in which MS lesions are clearly contrasted with normal brain tissue, while the cerebrospinal fluid and brain tissue contrast is diminished.¹² As interest grows in quantitative analyses of MS lesion load (see below), the optimization of image acquisition has become an area of active research.¹³

GADOLINIUM ENHANCEMENT

Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), which is used as a contrast agent in MRI scans, enhances the relaxation of hydrogen nuclei.¹⁴ Gadolinium-diethylenetriamine pentaacetic acid enhancement has more effect on T_1 relaxation, which is determined by the characteristics of the magnetic field, than on T_2 relaxation, which depends on interactions between the hydrogen nuclei and other macromolecules.¹⁴ The Gd-DTPA-enhanced MRI can detect new, asymptomatic lesions in patients with active MS,¹⁴ as well as lesions

correlated with new symptoms.^{15,16} On repeated scans, new lesions initially demonstrated with Gd-DTPA do not retain their enhanced appearance, suggesting that Gd-DTPA is a marker of blood-brain barrier impairment that is characteristic of new lesions.¹⁴ Serial Gd-DTPA-enhanced MRI scans show characteristic changes in the appearance of lesions over time: new lesions have a bright center, which is subsequently replaced on later images by a hyperintense ring.¹⁷ The Gd-DTPA-enhanced MRI also detects new spinal cord lesions in patients with active MS.¹⁸ Increasing the dose of Gd-DTPA used has been shown to increase the number of enhancing lesions detected on MRI scans.^{19,20}

APPEARANCE OF MS LESIONS ON MRI SCANS

As shown in the Figure, the plaques of MS appear as multiple, periventricular, rounded, or oval areas of increased signal intensity on T_2 -weighted MR images.²¹⁻²⁴ However, these lesions are not specific to MS and must be differentiated from others such as those of ischemic white matter lesions or normal aging.²²⁻²⁴ The MS lesions often have irregular outlines, a lumpy-bumpy appearance, small size, and a characteristic radial orientation.²²⁻²⁴ They may appear homogeneous or possess a thin rim of altered signal intensity.²⁵ Similar lesions are seen in the brainstem and spinal cord,^{26,27} al-

though sensitive imaging techniques for MRI of the spinal cord have been developed only recently.^{28,29} Spinal cord plaques are generally confined to no more than 2 vertebral segments, and atrophy or swelling is common only among longer plaques.²⁸ Clinical disability correlates with the presence of cord atrophy.³⁰

Three types of lesions have been described: new lesions, reappearing lesions, and enlarging lesions. In serial MRI studies, lesion activity was greater than clinical activity in all cases.³¹ New MS lesions generally evolved slowly during 4 to 6 weeks, followed by a gradual decrease in size over the subsequent 10 to 14 weeks.³¹

In studies using Gd-DTPA enhancement, new lesions typically appear first on Gd-DTPA-enhanced T₁-weighted images, indicating that blood-brain barrier impairment is an early event in the process of lesion formation.^{14,32-34}

CORRELATION BETWEEN PATHOLOGICAL AND MRI FINDINGS

Correlations between the pathological appearance of MS lesions (demyelination, perivascular inflammation, edema, macrophage infiltration, gliosis, axon loss, and necrosis)^{25,31} and MRI findings were first demonstrated in 1984 by Stewart et al.³⁵ Variation of signal intensity on T₁-weighted images correlated with the degree of lesion inflammation, demyelination, and gliosis.³⁶

Some insights into the pathophysiological correlates of lesion evolution were provided in a serial MRI study in which lesion development was followed with both Gd-DTPA-enhanced T₁-weighted images and proton-density images.¹⁷ Most lesions showed central hyperintensity on both scans at initial appearance. This pattern subsequently changed to one of ring hyperintensity, usually within 1 month of first appearance. The ring hyperintensity gradually faded over time.¹⁷ Although the evolution pattern varied from lesion to lesion, it was suggested that the early central hyperintensity phase might be related to the demyelination of oligodendroglia

lia accompanied by cellular infiltration and an expansion of the extracellular spaces that have been observed on electron microscopy studies of MS plaques and, on contrast-enhanced images, to the impairment of the blood-brain barrier at that location.¹⁷

QUANTIFICATION OF MS LESIONS

The MRI studies can provide quantitative information about MS lesions with respect to lesion number^{15,16,18,32,34,37-42} and lesion volume.^{4,43-48} Lesion number has not been related in a linear fashion to clinical symptoms, however, and serial MRI studies that follow up patients with MS often report development of new lesions without accompanying clinical symptoms, while new clinical symptoms may have no MRI correlates.^{16,18,32,34,37,38,41,49} The disappearance or diminution of previously observed lesions on later scans complicates assessments based on lesion number,^{32,40,49,50} as do characteristic changes in lesion appearance over time.¹⁷

Lesion volume may be calculated in various ways, but 2 general approaches are common: manual tracing of lesion outlines^{4,31,51} and semiautomatic lesion detection based on signal intensity.^{13,43-46,52-55}

One study⁴⁸ recently addressed the problem of standardizing data reported from multiple centers using a technique in which digitized images, stored on tape or film, are analyzed at a central processing center following a standard image analysis and segmentation procedure.

Multiparametric segmentation techniques, which require integration of 2 or more MRI sequences, are the newest method.¹³ In one study,⁵⁶ for example, proton-density and T₂-weighted sequences and T₁- and T₂-weighted images were combined and used to calculate lesion area.⁴⁷ These approaches provide more precise measurements of lesion load but need to be validated in MS.

Although quantitative measures based on MRI scans are now standard in many MS studies, the method remains imperfect. As

Filippi et al¹³ observed in a recent review of quantitative MRI, the quantitative assessment of brain abnormalities by MRI is reliable and reproducible, but further refinements are needed to improve the correlation between MRI abnormalities and clinical progression.

MRI: CONTRIBUTIONS TO UNDERSTANDING MS

Diagnosis of MS With MRI

Although the diagnosis of MS is generally made on clinical grounds,⁵⁷ MRI evidence may be used to support or suggest a diagnosis in cases that do not meet all clinical criteria. Several sets of MRI diagnostic criteria have been developed.^{58,59} The diagnostic criteria of Paty et al⁵⁸ include the presence of 3 lesions greater than 3 mm in diameter and 1 periventricular lesion, or the presence of 4 lesions greater than 3 mm. The criteria of Fazekas et al⁵⁹ require the presence of 2 of 3 findings: lesion size greater than 6 mm, lesions abutting the lateral ventricles, and lesions in the posterior fossa. These criteria⁶⁰ have a higher specificity and a lower false-positive rate.

MRI as a Prognostic Tool

In certain clinical settings, MRI has been proved to predict the development of MS. In the Optic Neuritis Treatment Trial,⁶¹ which enrolled 389 patients with optic neuritis but without definite or probable MS, the strongest indicator of risk for development of definite MS was MRI scan grade at study entry (**Table 1**), with 27 (30.3%) of 89 patients with grade 4 scans (on a 0-5 grade ranking system) developing MS by 2 years compared with 8 (4.9%) of 163 patients with grade 0 scans.

Similar results were reported by the MS Nuclear Magnetic Resonance Research Group⁶² in a 5-year follow-up study of 89 of 132 patients who initially presented with an acute, clinically isolated syndrome of the optic nerve, brainstem, or spinal cord. Brain lesions at initial presentation were associated with a relative risk of 6.8 ($P < .005$) for developing MS.⁶³ After 5 years,

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41 (72%) of 57 patients with abnormal initial MRI scans had developed definite MS in comparison with only 2 (6%) of 32 patients with normal initial scans (relative risk, 87; $\chi^2=36.8$; $P<.0001$).⁶²

It is thus apparent that MRI lesion data at presentation are useful in predicting the subsequent development of MS in patients with clinically isolated syndromes and may identify patients who will benefit most from early treatment, with monitoring of their course.¹³

Lesion Load and MS Type

Patients with chronic-progressive MS generally have a higher mean lesion load overall than those with benign MS.⁴ However, 20% of patients with benign MS have individual lesion loads higher than those with chronic-progressive MS.⁴ Patients with chronic-progressive MS have more infratentorial lesions but a similar number of supratentorial lesions as patients with benign MS.⁴

In a 6-month serial Gd-DTPA-enhanced MRI study,¹⁶ more new lesions and more Gd-DTPA-enhanced lesions developed in patients with relapsing-remitting MS than in patients with benign MS.

Lesion Load: Relationship to Clinical Status

Establishment of a usable relationship of MRI-quantified MS lesion load to the clinical status of patients with MS is influenced by a number of methodological difficulties.¹³ These problems include the use of disability scales, such as the EDSS, that measure spinal cord disease; the difficulty in measuring spi-

nal cord lesions with MRI; the inclusion of patients with varying durations of disease; the short-term nature of most studies; and the technical difficulties in measuring lesion load reproducibly and reliably.^{3,13,64}

Studies Conducted Without Contrast Enhancement. The correlation between lesion load, measured by unenhanced MRI, and clinical disability was studied in 53 patients with suspected MS.⁶⁵ Lesion burden (rated on a 5-point graded scale) was significantly correlated with clinical disability on all 3 rating scales, with the strongest correlations between the EDSS and Neurologic Rating Scale scores ($P<.001$).⁶⁵

Two small studies,^{32,49} both on patients with MS with mild disability (EDSS score, ≤ 3.0 at study entry), failed to find any correlation between lesion development and clinical signs or symptoms. In a 6-month study of 281 patients with all forms of clinically definite MS (mean EDSS score at entry, 3.5) over 24 to 36 months, Filippi and coworkers⁶⁶ reported an increased number of active lesions, which were correlated with changes on the EDSS for all patients.

Double-echo images with automatic segmentation and image registration were used to extract lesion volumes and counts in a recent serial study of 45 patients with MS.⁶⁷ Correlations were found between clinical measures (EDSS, Ambulation Index, or attacks) and each of the following: change in lesion volume, change in number of lesions, cumulative change in volume of lesions, and cumulative change in number of lesions.⁶⁷

Studies Conducted With Contrast Enhancement. A number of studies^{14,33,34,38} using Gd-DTPA-enhanced MRI have found that the appearance of new MS lesions precedes the development of new clinical symptoms in patients with stable MS.

Several small studies^{15,16,68} found that Gd-DTPA-enhanced MS lesions corresponded to new signs or symptoms. The correlation between increased activity on MRI scans and clinical worsening in 9 patients with relapsing-remitting MS during 24 to 37 months was assessed with a logistic regression analysis model. Enhancing new lesion number and total area of enhancement had significant predictive effects on all months of EDSS score increase ($P=.007$, $P=.004$, and $P=.002$).⁴⁴ In a study³⁹ in which serial monthly Gd-DTPA-enhanced MRI scans and clinical evaluations were obtained in 10 patients with relapsing-remitting MS and 2 patients with chronic-progressive MS during a 12- to 55-month period, "bursts" of lesion number and area above the mean for an individual patient were usually accompanied by an increase of 0.5 or higher on the EDSS and clinical worsening.

Similarly, change in the number of enhanced and unenhanced lesions on Gd-DTPA-enhanced MRI scans and change in the EDSS and Ambulation Index scores were correlated in a 1-year study of 18 patients with definite MS.⁴⁰ In 234 pairs of MRI, EDSS, and Ambulation Index measurements, we found positive correlations between change in the number of lesions and change in EDSS ($P<.001$) and Ambulation Index ($P<.001$) scores. The cumulative number of new lesions and deterioration on the EDSS ($P<.005$) or Ambulation Index scale ($P<.001$) were also correlated (**Table 2**).⁴⁰

Thorpe and colleagues¹⁸ followed up 10 patients with relapsing-remitting MS for 1 year with serial Gd-DTPA-enhanced MRI scans of the spinal cord and brain and evaluations of relapse and disability. New lesion activity in the brain and spinal cord were found to be strongly correlated ($\chi^2=10.36$; $P<.002$), and new spinal cord lesions were significantly more likely to be associated

with clinical symptoms than were new brain lesions ($P < .0001$, Fisher exact test).¹⁸

Most recent studies that have found correlations between lesion activity on MRI scans and clinical disease progression have been serial studies (**Table 3**), an observation that suggests that cross-sectional studies may miss such correlations because of heterogeneity in the apparent lesion load between patients. It is likely that the development of more refined imaging technologies will lead to the discovery of even stronger correlations between neurological activity and clinical outcome.

Lesion Load and Cognitive Function

Multiple sclerosis affects cognitive as well as physical functioning, and the relationship between cognitive function and lesion load in patients with MS has been examined in several studies. The extent of corpus callosum atrophy on MRI scans was shown to be significantly correlated with dementia ($P < .001$).^{69,70} Total lesion load also correlated with cognitive function.⁷⁰⁻⁷² Moreover, the pattern of cognitive impairment in MS depends on the location of the cerebral lesions, with frontal lobe lesions correlating with impaired conceptual reasoning.⁷³

MRI as a Measure of Outcome in MS Clinical Trials

Traditional measures of treatment outcome in MS involve clinical events such as relapse frequency or worsening of disability. Because the course of MS is highly variable, trials using such end points must enroll large numbers of patients and follow them up for several years. In addition, available clinical scales are not entirely satisfactory with respect to interrater reliability and bias. For these reasons, there has been a great interest in developing an effective surrogate marker of MS activity.⁷⁴

Of the available imaging and immunological measures that may provide MS marker data, MRI is the most widely used. Guidelines for MRI use in the monitoring of treat-

ment of MS were published in 1991,³ and most clinical trials of MS include MRI as a measure of therapeutic outcome. However, because lesion activity on MRI scans may not correlate with clinical findings, serial MRI is currently recommended as a secondary outcome measure of pathological progression in clinical trials involving patients with established MS.⁷⁴

Cyclosporine Trials. Two cyclosporine trials^{75,76} have been conducted in patients with MS. In the first,⁷⁵ both MRI and clinical disability as measured by the EDSS were used to compare the effects of cyclosporine and azathioprine in 74 patients with definite MS; both treatments appeared to be equally effective, but neither halted neurological progression as evidenced by the appearance of new lesions. In the second study,⁷⁶ MRI data were used to compare the efficacy of cyclosporine and placebo in 157 patients with chronic-progressive MS; although a marked increase in lesion load was seen during the study period, treatment with cyclosporine did not affect lesion load.

Interferon Alfa Trials. The efficacy of interferon alfa in the treatment of MS has been evaluated in 2 randomized, double-blind, placebo-controlled trials.^{77,78} In 100 patients with chronic-progressive MS given human lymphoblastoid interferon or placebo for 6 months, serial MRI scans obtained prior to treatment and at 6 and 24 months showed treatment did not affect the mean total lesion load at 6 or 24 months, but a trend toward improve-

ment (change from baseline) in lesion load was seen in more patients treated with interferon alfa than with placebo at 6 months ($z = 1.96$; $P = .05$).⁷⁷

In a pilot trial⁷⁸ in which 20 patients with relapsing-remitting MS were randomized to receive high doses of recombinant interferon alfa-2A or placebo, fewer clinical exacerbations were observed in the recombinant interferon alfa-2A group than in the placebo group, and the mean number of active lesions (new or enlarging) on MRI scans in the recombinant interferon alfa-2A group was significantly lower than that in the placebo group ($P < .01$).

Interferon Beta-1B Trial. The efficacy of interferon beta-1B in the treatment of relapsing-remitting MS has been evaluated in a large, randomized, placebo-controlled, double-blind multicenter trial of 372 patients.^{51,79,80} The mean percentage change in lesion area on annual MRI scans decreased significantly at year 1, 2, and 3 in the interferon beta-1B group, compared with increases in the placebo group; at year 3, the mean percentage change in the placebo group was +17.1% while that for the interferon beta-1B group was -6.2% ($P = .002$).⁵¹ In the fourth and fifth years of this study, the median percentage change in MRI lesion area from baseline continued to increase each year in the placebo group and to decrease or remain stable in the interferon beta-1B group.⁸⁰

Serial scans obtained at 6-week intervals in 52 patients to determine lesion activity showed that the interferon beta-1B group had a median of 5.9% active scans while

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Table 3. Serial MRI Studies in Patients With MS: Correlations Between Neurological and Clinical Activity*

Source, y	No. of Patients	EDSS Score at Entry	No. of Scans per Patient	Use of Gd-DTPA	Neurological and/or Clinical Correlations
Edwards et al, ⁶⁵ 1986	53	2.5-5.6	1	No	Positive correlation between lesion grade and clinical disability
Isaac et al, ⁴⁹ 1988	7	Mean, 3.0	5	No	No correlation between new or enlarging lesions and new clinical symptoms
Koopmans et al, ⁴ 1989	8	5.0-7.0	Median, 12	No	Lesion activity (new, enlarging, reappearing lesions) was not correlated with clinical relapse or new neurological signs
Willoughby et al, ³² 1989	9	0-1.5	Mean, 10	No	No correlation between new or enlarging lesions and new clinical signs or symptoms
Filippi et al, ¹⁹ 1995	281	Mean, 3.5	2	No	Correlation between new, enlarging, and all active lesions and change in EDSS score
Gonzalez-Scarano et al, ¹⁵ 1987	16	NR	1	Yes	Correlation between new enhancing lesions and new signs or symptoms in patients with active disease
Grossman et al, ⁶⁸ 1988	13	NR	2	Yes	4 of 6 patients had new clinical activity correlated with enhancing lesions on most recent MRI scan
Harris et al, ³⁸ 1991	6	Mean, 1.9	Median, 11	Yes	New enhancing lesions seen in all patients; new lesions did not correlate with symptoms or relapse (2 patients)
Thompson et al, ¹⁶ 1992	10	Mean, 3.0	6-12	Yes	No. of new events on MRI scans significantly related to clinical activity ($P<.01$)
Smith et al, ⁴⁴ 1993	9	1.5-3.5	24-37	Yes	No. of lesions (unenhanced and enhanced) and enhancement area significantly greater in months of EDSS score increase; lesion activity on all MRI parameters predicted clinical deterioration
Frank et al, ³⁹ 1994	12	1.5-6.5	12-55	Yes	"Bursts" of enhancing lesions associated with increase ≥ 0.5 in EDSS score; no correlation between average MRI parameters and EDSS scores
Khoury et al, ⁴⁰ 1994	18	1.0-6.5	24	Yes	Positive correlations: change in lesion number and change in EDSS and AI scores; change in enhancing lesion number and change in EDSS and AI scores; change in cumulative lesion number and deterioration in EDSS or AI scores
Thorpe et al, ¹⁸ 1996	10	Median, 2.5	12	Yes	Of 19 new spinal cord lesions, 6 (5 enhancing) were correlated with new symptoms vs 1 of 167 new brain lesions ($P<.001$, Fisher exact test)

*MRI indicates magnetic resonance imaging; MS, multiple sclerosis; EDSS, Expanded Disability Status Scale; Gd-DTPA, gadolinium-diethylenetriamine pentaacetic acid; NR, not related; AI, Ambulation Index.

the placebo group had a median of 29.4% active scans, a median reduction of 80% ($P=.006$).⁵¹

Interferon Beta-1A Trial. In this trial⁸¹ of 301 patients randomized to receive interferon beta-1A or placebo, disease activity was measured by annual Gd-DTPA-enhanced MRI scans. At 1 year, the proportion of positive scans dropped to 29.9% (from 52.5% at baseline) in the interferon beta-1A group and 42.3% (from 53.8% at baseline) in the placebo group; the proportion of active scans was significantly lower in the interferon beta-1A group ($P=.05$).⁸¹

Advanced Applications of MRI in MS

The technical difficulties involved in imaging MS lesions reliably and reproducibly have led to the development of newer techniques with greater powers of discrimination than conventional MRI (T_1 -

weighted, T_2 -weighted, and proton-density images).

Fluid-Attenuated Inversion Recovery Pulse Sequence. Fluid-attenuated inversion recovery uses a long inversion time to suppress the MRI signal from cerebrospinal fluid plus heavy T_2 weighting of the image obtained with a long echo time. Although this technique requires more time than conventional MRI, detection of lesions is improved.^{82,83} Fluid-attenuated inversion recovery has also been used to facilitate the visualization of brainstem lesions, including those in MS, that were not visible on conventional MR images.⁸⁴

Magnetization Transfer Imaging. Magnetization transfer imaging identifies the water content of the imaged material and its relationship to macromolecules or tissue membranes, thus producing an image that can distinguish new lesions surrounded by edema and

chronic, highly demyelinated, or gliotic lesions.⁸⁵ Several magnetization transfer imaging studies^{86,87} have suggested that white matter abnormalities, as measured by magnetization transfer ratio, are present in normal-appearing tissue. Magnetization transfer ratios from normal-appearing white matter in patients with MS are lower than those in control subjects.^{86,87} In addition, magnetization transfer ratios appear to be different among patients with different forms of MS.⁸⁷

Magnetic Resonance Spectroscopy. Proton magnetic resonance spectroscopy and magnetic resonance spectroscopy imaging can be used to measure metabolic changes in the white matter of patients with MS.⁸⁸ The proton spectra of normal human brain at long echo time is dominated by 3 peaks: *N*-acetylaspartate, choline, and creatine. The creatine peak remains relatively stable except in the largest acute

plaques. Decreases in the *N*-acetylaspartate-creatine ratio in MS lesions may indicate loss of neuronal viability,⁸⁹ whereas increases in the choline-creatine ratio and inositol levels may indicate myelin breakdown.⁹⁰ Distinct peaks in the lipid region seen in selected plaque-containing regions may be correlated with recent clinical or MRI-defined disease activity.⁹¹ Magnetic resonance spectroscopy imaging has been used to evaluate axonal damage in 35 patients with MS and 16 normal controls.⁸⁹ Serial MRI and magnetic resonance spectroscopy imaging performed at 6-month intervals showed a decrease in the *N*-acetylaspartate values of MS lesions over time; the reduction was greater in patients with chronic-progressive MS than in those with relapsing-remitting MS.⁸⁹

Hypointense Lesions on T₁-Weighted Images (Black Holes). Hypointense lesions on T₁-weighted images were first described by Uhlenbrock and Sehlen,⁹² who hypothesized that they represented areas of axonal loss and gliosis. More recently, the degree of hypointensity of these black holes appeared to correlate with magnetization transfer ratios, suggesting that increasing lesion hypointensity corresponds to additional breakdown in the macromolecular structure of myelin.⁹³⁻⁹⁵ Thus, hypointense lesions on T₁ MRI scans may represent the more disabling lesions. In a preliminary postmortem study,⁹⁶ the degree of hypointensity of T₁ lesions was found to correlate with axonal loss. In a cross-sectional analysis⁹⁷ comparing T₁ and T₂ lesion loads as they correlate to EDSS, T₁ lesion load had a higher correlation with EDSS for both patients with relapsing-remitting and secondary-progressive MS. However, the technique for quantification of T₁ lesion load needs to be further defined.

CONCLUSIONS

Magnetic resonance imaging has become a powerful tool for the study of MS, with practical applications in diagnosis and prediction of prognosis and with research applications in the study of MS natural history. In

addition, MRI is now included as an adjunctive measure in clinical trials of new treatments for MS.¹³ The correlation between lesions observed on MRI scans of patients with MS and pathological findings noted on autopsy or biopsy is well established.^{25,36} The MRI scans can be used not only to identify neurological abnormalities in MS but also to quantify those abnormalities.

Conventional MRI is the method of choice for the diagnosis of MS.³¹ For the general practitioner, regular T₁-weighted and T₂-weighted images should be sufficient for the diagnosis of MS. In clinical trials, however, clinical changes are not consistently related to MRI changes. In part, such differences are related to differences in study methodologies, including the MRI parameters and the method of quantitation used, as well as different measures of clinical disability and progression.

Newer MRI techniques may eventually overcome some of the current limitations. It is hoped that such new technologies may eventually be used in conjunction with conventional MRI to permit more accurate staging of lesions and disease and to gauge the progress of disease in patients with MS.

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Reprints: Samia J. Khoury, MD, Center for Neurologic Diseases, Brigham and Women's Hospital, 77 Ave Louis Pasteur, HIM 714, Boston, MA 02115 (e-mail: khoury@cnd.bwh.harvard.edu).

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Correction

Errors in Tables and Text. In the article titled "The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," published in the November 24, 1997, issue of the ARCHIVES (*Arch Intern Med*. 1997;157:2413-2446), the following corrections should be noted: page 2421, line 20 under the "Lifestyle Modifications" section, reference citations should read "77C, 78Ra"; page 2422, reference line at the bottom of column 3 should read "77C, 78Ra, . . ."; page 2426, Table 8, column 3, parenthetical dosing frequency for Moexipril should read "(1-2)"; page 2433, Table 15, the title should read "Ninety-fifth . . ."; page 2442, reference 140, the volume number should read "350"; and on page 2444, reference 209, the code "M" should appear at the end of the reference. The journal regrets the errors.