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.

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

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 patients subsequently develop a form of MS that is marked by a progressive decline in neurological function for longer than 6 months; 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. 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
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 T1 relaxation time.11 The T2 relaxation time is the time it takes for the hydrogen nucleus to lose the energy that keeps it aligned within the original magnetic field. T2 is always shorter than T1.11

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 T1 and T2 components of the image, which is determined by the radiofrequency pulse sequence.11 On T1-weighted images, tissues with a short T1 appear brighter than those with a long T1, while on T2-weighted images, tissues with a long T2 appear brighter than those with a short T2.11 Proton-density images (with characteristics between those of T1- and T2-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-DPTA), 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 T1 relaxation, which is determined by the characteristics of the magnetic field, than on T2 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 T2-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.23 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. \cite{20,29} Spinal cord plaques are generally confined to no more than 2 vertebral segments, and atrophy or swelling is common only among longer plaques. \cite{28} Clinical disability correlates with the presence of cord atrophy. \cite{30}

Three types of lesions have been described: new lesions, reap- pearing lesions, and enlarging lesions. In serial MRI studies, lesion activity was greater than clinical activity in all cases. \cite{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. \cite{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. \cite{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) \cite{15,31} and MRI findings were first demonstrated in 1984 by Stewart et al. \cite{35} Variation of signal intensity on T1-weighted images correlated with the degree of lesion inflammation, demyelination, and gliosis. \cite{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. \cite{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. \cite{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 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. \cite{17}

**QUANTIFICATION OF MS LESIONS**

The MRI studies can provide quantitative information about MS lesions with respect to lesion number, \cite{15,16,32,34,37,38} and lesion volume. \cite{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. \cite{16,32,34,37,38,41,49}

The disappearance or diminution of previously observed lesions on later scans complicates assessments based on lesion number, \cite{32,40-49} as do characteristic changes in lesion appearance over time. \cite{17}

Lesion volume may be calculated in various ways, but 2 general approaches are common: manual tracing of lesion outlines \cite{4,31} and semiautomatic lesion detection based on signal intensity. \cite{13,35-36,52-53}

One study \cite{48} 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 procedure.

Multiparametric segmentation techniques, which require integration of 2 or more MRI sequences, are the newest method. \cite{13}

In one study, \cite{56} for example, proton-density and T2-weighted sequences and T1- and T2-weighted images were combined and used to calculate lesion area. \cite{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 al. \cite{13} 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, \cite{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. \cite{58,59} The diagnostic criteria of Paty et al. \cite{58} 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 al. \cite{59} 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 criteria \cite{60} have a higher specificity and a lower false-positive rate.
Lesion Load and MS Type

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

In a 6-month serial Gd-DTPA–enhanced MRI study, 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. These problems include the use of disability scales, such as the EDSS, that measure spinal cord disease; the difficulty in measuring spinal 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.

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. 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).

Two small studies, 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 coworkers 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. 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.
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.69-72 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 treatment 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 pathologic progression in clinical trials involving patients with established MS.74

Cyclosporine Trials. Two cyclosporine trials75,76 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 neurologic 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 improvement (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 trial79 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.31,79,80 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).31 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
the placebo group had a median of 29.4% active scans, a median reduction of 80% (P = .006). The Interferon Beta-1A Trial. In this trial 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 53.8% at baseline) in the interferon beta-1A group and to 42.3% (from 53.8% at baseline) in the placebo group; the proportion of positive scans dropped to 29.9% (from 52.5% at baseline) in the interferon beta-1A group and to 42.3% (from 53.8% at baseline) in the placebo group; the proportion of positive scans dropped to 29.9% (from 52.5% at baseline) in the interferon beta-1A group and to 42.3% (from 53.8% at baseline) in the placebo group.

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

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

*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.

### 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 (T1-weighted, T2-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 T2 weighting of the image obtained with a long echo time. Although this technique requires more time than conventional MRI, detection of lesions is improved.

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.

**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. Several magnetization transfer imaging studies 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. In addition, magnetization transfer ratios appear to be different among patients with different forms of MS.

**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. 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
Hypointense Lesions on T1-Weighted Images (Black Holes).

Hypointense lesions on T1-weighted images were first described by Uhlenbrock and Sehlin, 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. Thus, hypointense lesions on T1 MRI scans may represent the more disabling lesions. In a preliminary postmortem study, the degree of hypointensity of T1 lesions was found to correlate with axonal loss. In a cross-sectional analysis 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. The correlation between lesions observed on MRI scans of patients with MS and pathological findings noted on autopsy or biopsy is well established. 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. 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.

Accepted for publication September 25, 1997.

This article was supported by an unrestricted educational grant from Berlex Laboratories, Richmond, Calif.

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).

REFERENCES


ARCH INTERN MED/VOL 138, MAR 23, 1998

©1998 American Medical Association. All rights reserved.