REVIEW ARTICLE

Multiple Sclerosis

What Have We Learned From Magnetic Resonance Imaging Studies?

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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. *Arch Intern Med. 1998;158:565-573*

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 patients subsequently develop a form of MS that is marked by a progressive decline in neurological function for longer than 6 months[4]; 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]

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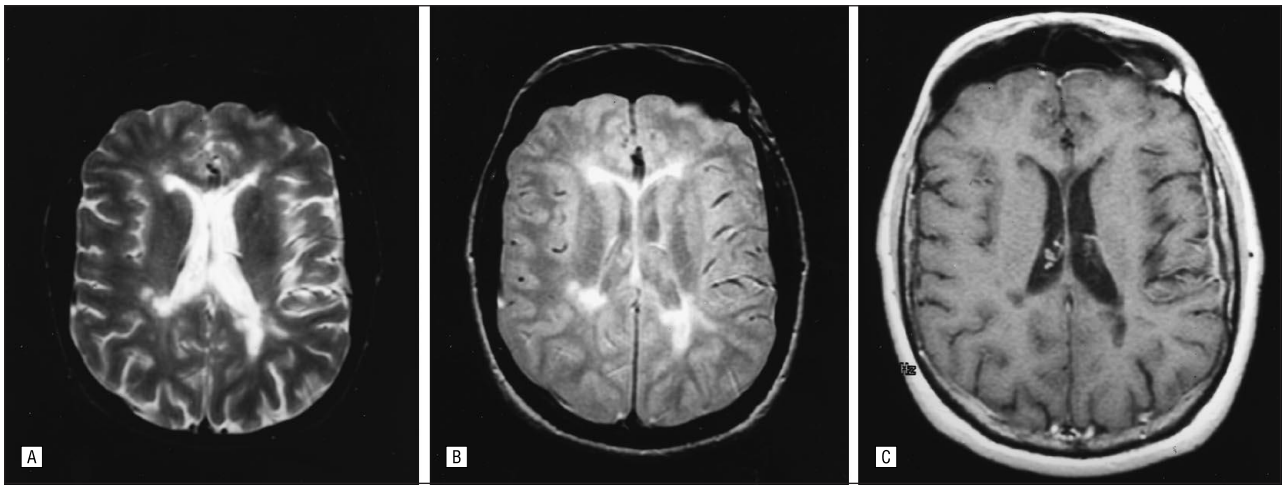

A slice of magnetic resonance imaging scan of a patient with multiple sclerosis showing characteristic periventricular lesions with increased signal on T_2-weighted (A) and proton-density (B) images. A gadolinium-enhanced magnetic resonance imaging scan did not show enhancing lesions, but some of the 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 characteristics 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-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 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 T_1-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 T_1-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 T_1-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 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 study[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 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 T_2-weighted sequences and T_1- and T_2-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 al[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,[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 al[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[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[60] 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 Group[62] 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,

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; χ^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 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.[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 coworkers[66] 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 study[39] 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 colleagues[18] 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 (χ^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 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 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 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 trial[78] 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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