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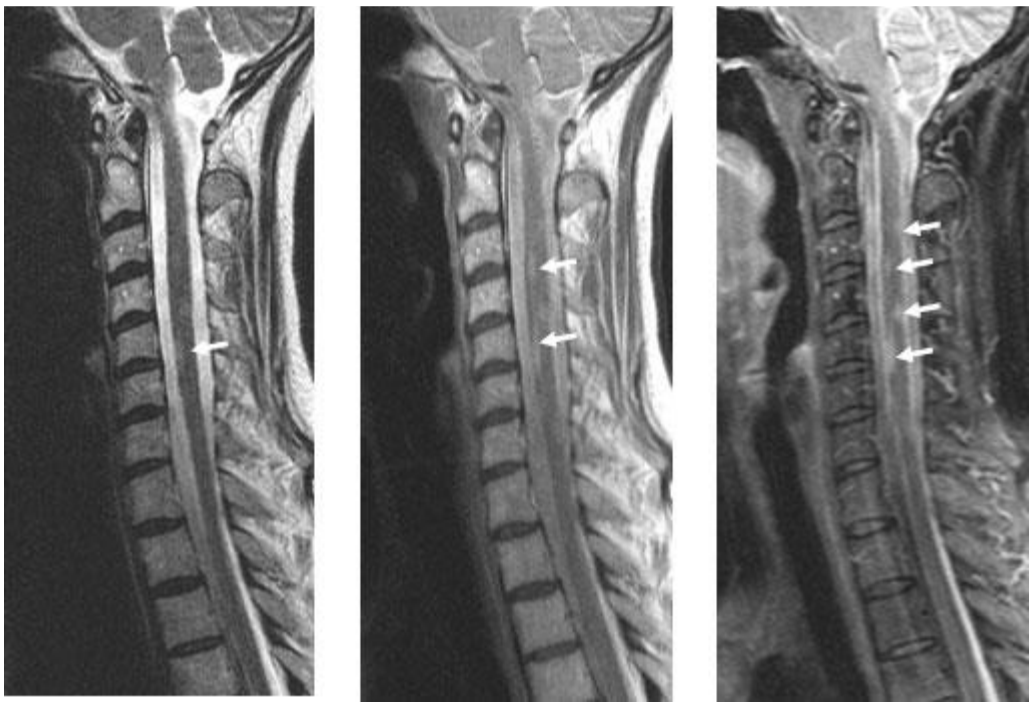
کتابچه راهنمای پزشکان - MRI

The Role of MRI in Multiple Sclerosis Diagnosis and Management



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Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS), which has been traditionally characterized by attacks of inflammatory cells that erode myelin and transect axons, interfering with neuronal transmission. In the absence of therapy, repeated attacks lead to an accumulation of structural brain damage, which manifests as physical and cognitive disability. Brain and spinal cord scars, which represent the "footprints" of MS attacks, were first only visible on pathologic specimens obtained at autopsy. The development of computed tomographic (CT) scans provided a significant advance in brain imaging over plain film x-rays, but was not sensitive to the pathologic changes of MS. The development of magnetic resonance imaging (MRI) finally enabled the identification of MS lesions and provides a powerful tool to assess MS disease activity and guide therapy (Figure 1).

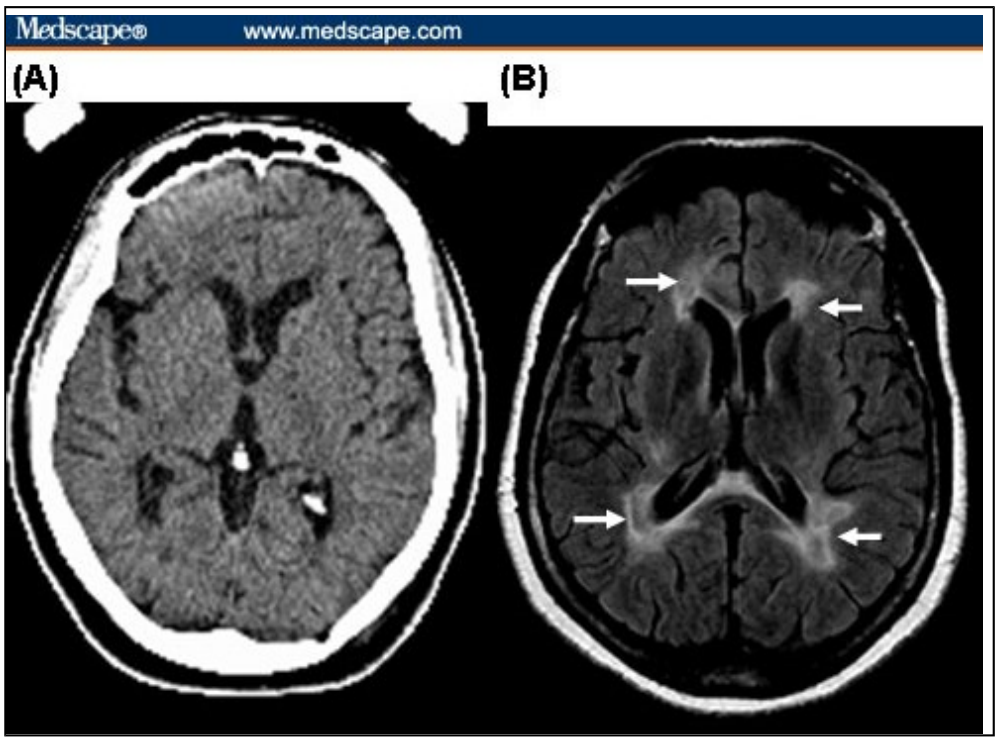

Figure 1. Comparison of CT and MRI images. (A) CT scan and (B) MRI showing the increased sensitivity that MRI adds in visualizing brain lesions, such as those in MS (arrows).

MRI: Understanding the Technology and Applications

MRI generates images with signals derived from the hydrogen protons of water, and consequently can be used to visualize all body tissues. Hydrogen protons, acting as tiny molecular bar magnets, are aligned by the powerful superconducting magnet in the donut-shaped MRI scanner. This magnet is left on, and is thousands of times stronger than the magnetic field of Earth. The aligned protons are then perturbed by radiofrequency (RF) waves generated by copper coils surrounding the patient. When the RF coils are turned off, the protons "relax" to their previously aligned state in the magnetic field, giving off a signal that is received by another set of coils that function much like an antenna. This repeated on-off-receive cycling of the RF coils happens hundreds of times per minute in modern scanners, and is what creates the loud repetitive banging or vibration noise that is heard when the scanner is operating. Protons in different environments (and packed together in different densities) react differently when perturbed by an RF pulse, and this variation generates contrast between different types of tissues.

In unweighted "proton density" images, signal intensity is directly proportional to hydrogen proton density. Image contrast can be further enhanced by "weighting" the image to capture more of either the longitudinal or transverse relaxation components, which are, respectively, called T1 and T2. Weighting the image focuses on specific characteristics of the tissue, and can be further manipulated through variations in the strength, orientation, and timing of RF pulses. T1-weighted imaging is best for defining anatomy (signal contrast appears similar to gross anatomic sections), whereas T2-weighted imaging is more sensitive to tissue edema, which appears bright, highlighting pathology (such as MS lesions, brain tumors, etc). T1-weighted imaging is also used after gadolinium contrast administration to identify certain structures or lesions. Gadolinium enhancement is readily identified as an intensely bright signal on an otherwise moderate-intensity image.

Characterization of MS Lesions With Conventional MRI

Conventional MRI (T1- and T2-weighted imaging and their variants) has greatly increased the sensitivity of diagnosing MS and assessing disease activity. This tool has led to earlier diagnosis, which has become especially important with the growing emphasis on early treatment with immunomodulatory therapies.

MS lesions on MRI occur most commonly in the white matter of the brain and spinal cord. Typical lesions are periventricular, oriented perpendicular to the long axis of the lateral ventricles, and are ovoid in shape. This morphology is commonly described as "Dawson's fingers" after histologist James W. Dawson who described the gross appearance of the cerebral lesions in 1916.[1] The corpus callosum is commonly affected and is best visualized on sagittal images. MS lesions can also appear in the brainstem, cerebellar hemispheres, and subcortical regions (affecting so-called U-fibers), findings that increase the specificity for MS over other multifocal CNS diseases. Although not usually apparent on conventional MRI, MS lesions have been shown by pathology and specialized imaging measures to commonly affect the cerebral cortex.[2]

The Evolution of MS Lesions on MRI

On conventional MRI, MS lesions go through a typical pattern of evolution.[3] With very frequent imaging, most lesions are identified in their earliest stage as robustly enhancing with gadolinium-based contrast agents, hyperintense on T2-weighted images and either isointense or hypointense on T1-weighted images (Figures 2 and 3). These gadolinium-enhancing lesions correspond pathologically to early active areas of inflammation and blood-brain barrier dysfunction. After the acute inflammatory stage, MS lesions will cease to enhance with gadolinium over 2-4 weeks. T2 lesions persist, sometimes with hypointensity, on T1 images.

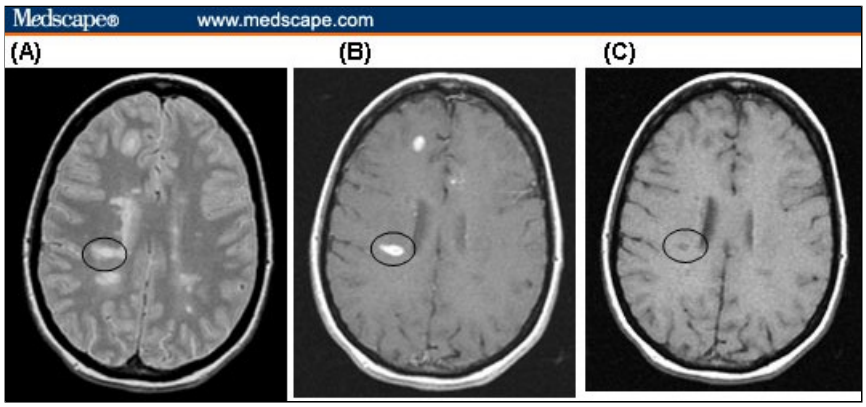

Figure 2. MS lesions on conventional MRI. Circled is an active lesion, showing (A) hyperintensity on T2-weighted images; (B) hyperintensity on postgadolinium T1-weighted images; and (C) hypointensity on T1-weighted images without gadolinium.

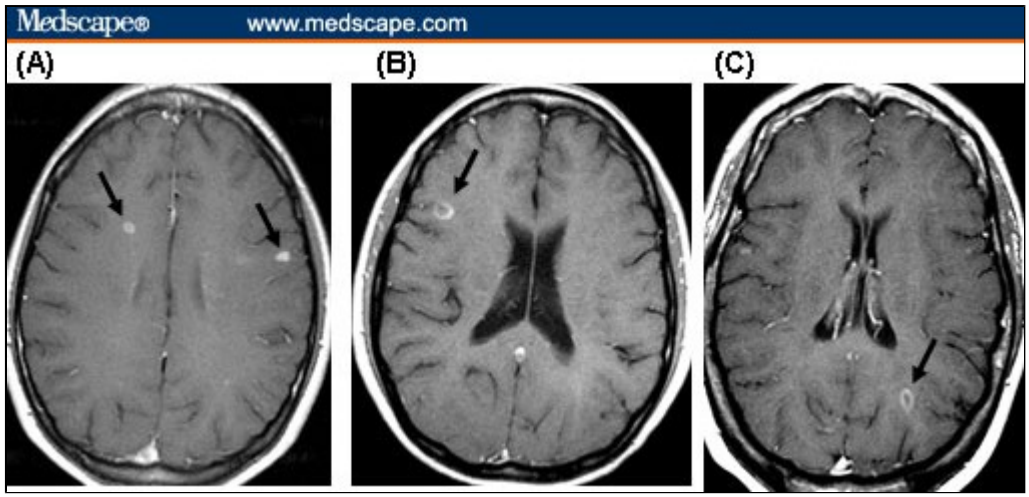

Figure 3. Gadolinium-enhancing lesion morphology. Solid lesions are shown in (A), an open-ring lesion in (B), and a closed-ring lesion in (C).

T2-weighted imaging at traditional magnetic field strengths is very sensitive to tissue edema, and therefore is useful for visualizing acute and chronic MS lesions. Lesions that appear bright on T2-weighted images represent T2 prolongation due to any of a variety of tissue changes, including edema, gliosis, inflammation, demyelination, remyelination, and axon loss. Because this relatively broad range of pathologic changes leads to a common appearance on T2-weighted images, a given lesion typically persists in the T2 hyperintense stage for many years, and lesions on T2-weighted images are the most commonly recognized lesions associated with MS. Fluid-attenuated inversion recovery (FLAIR) is a technique of acquiring a T2-weighted image with a suppressed cerebrospinal fluid (CSF) signal, which is useful for detecting subcortical and periventricular lesions otherwise obscured by the CSF signal on T2-weighted images (Figure 4).[4] Because of its high sensitivity, FLAIR imaging frequently highlights small tissue abnormalities that can be present as normal variants with aging or in relatively benign conditions, such as migraine headache (Figure 5). Traditional fast spin-echo T2-weighted images remain the most specific for lesion identification in the posterior fossa, where FLAIR is subject to artifacts.[5]

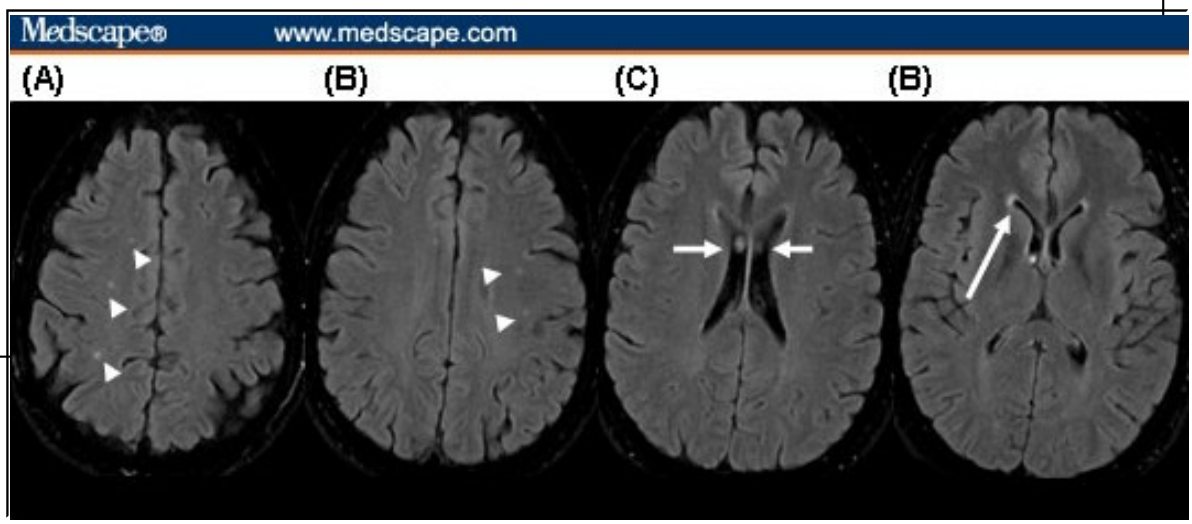

Figure 4. FLAIR variants and artifacts. Small peripheral hyperintensities on FLAIR MRI (arrowheads in [A] and [B]) can be seen in normal aging or patients with migraine headaches. Intraventricular pulsation artifact (arrow, [C]) occurs in areas of fast-flowing CSF, such as near the foramen of Monro or the fourth ventricle. Ventricular "capping" (arrow, [D]) is a normal finding that occurs at the frontal and posterior horns of the lateral ventricles and is important to distinguish from the periventricular lesions of MS.

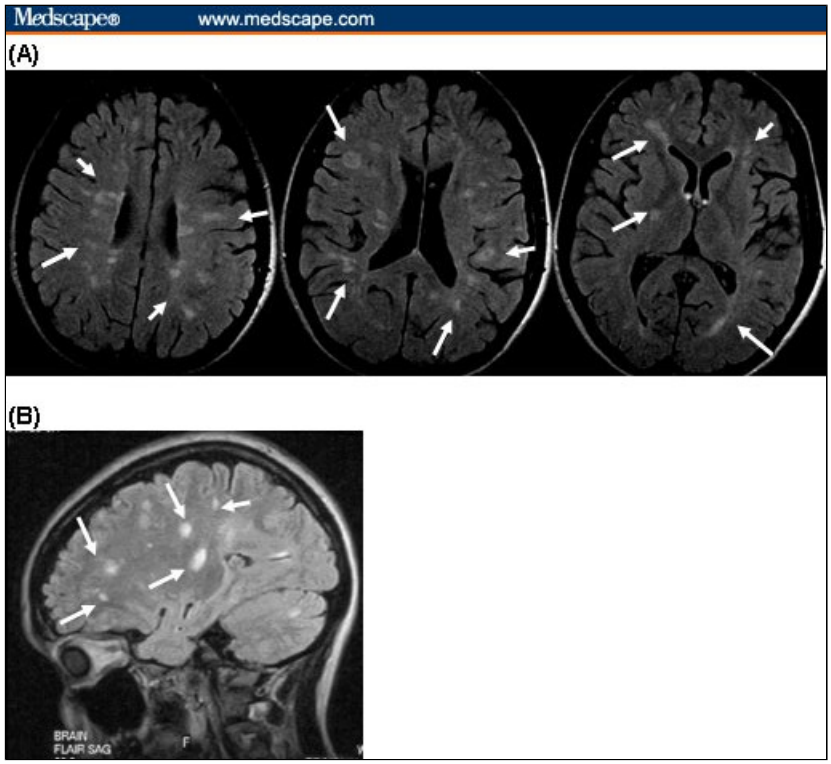

Figure 5. Typical changes of MS in the brain on axial and sagittal FLAIR T2 images. (A) Typical changes on axial FLAIR images. Note the periventricular ovoid lesions oriented perpendicular to the lateral ventricle, and lesions in the corpus callosum, with predilection for the frontal and posterior horns. (B) A sagittal FLAIR image, a useful sequence for identifying MS lesions.

In the spinal cord, variations on T2-weighted images are used in order to increase the sensitivity of detecting pathology (Figure 6). The spinal cord's small cross-sectional size in relation to the surrounding tissues poses a technical challenge in MRI. Proton density images offer increased lesion contrast over traditional T2-weighted images in the spinal cord. Short tau inversion recovery (STIR) imaging is used to suppress signal from fatty tissue, such as healthy, myelinated white matter tracts; its other effects increase MS lesion contrast within the spinal cord. STIR has been shown to be the most sensitive technique for identifying MS lesions in the spinal cord, and may be the best technique for identifying very chronic MS lesions that are invisible with other techniques.[6]

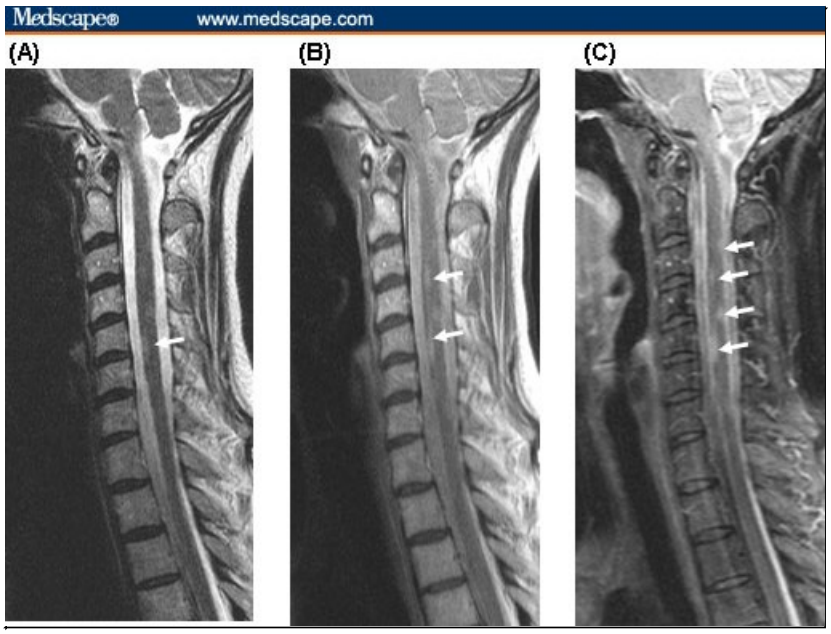

Figure 6. T2-weighted spinal cord images. (A) Traditional T2, (B) proton density, and (C) STIR images of the spinal cord of an MS patient. STIR images are most sensitive for detecting MS lesions.

Lesions that are hypointense on T1-weighted images ("T1 black holes") represent the most severe, chronic stage of MS lesions, characterized pathologically by irreversible tissue loss and axonal destruction (Figure 7).[7] Up to half of all gadolinium-enhancing lesions will persist as chronic T1 black holes, making the presence of gadolinium-enhancing lesions a strong predictor of long-term development of T1 black holes.[8] T1 black holes correlate significantly with the future development of whole-brain atrophy, suggesting that axonal injury contributes significantly to brain atrophy development.[9-11]

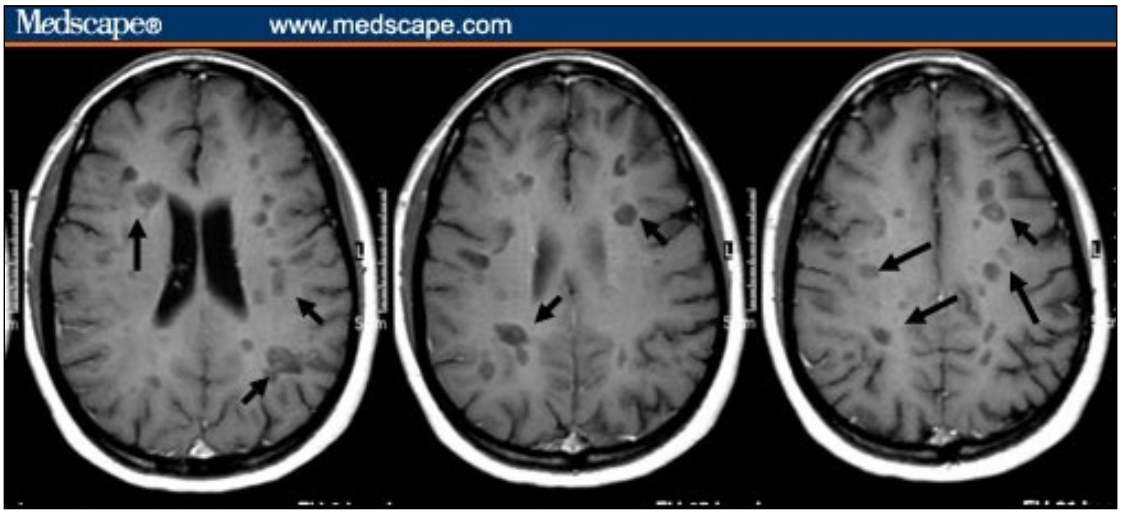

Figure 7. T1 black holes. The patient has a large burden of T1 hypointense lesions ("black holes"), which indicate areas of irreversible tissue loss and axonal destruction.

The Diagnosis of MS and the Role of MRI

MS was traditionally diagnosed after multiple clinical events separated in time and space (ie, different area of the CNS) without other identifiable cause.[12] Using these "Poser criteria," patients with a single clinical attack and an otherwise typical brain MRI for MS were left waiting for their "second event" before they could be diagnosed with definite MS. This situation left patients and clinicians with uncertainty in regard to the underlying diagnosis, and denied patients appropriate treatment with MS therapies.

Findings from MRI were officially incorporated into the diagnostic criteria of MS in 2001, called the International Panel Criteria.[13] The diagnostic criteria for the primary progressive form of MS were also outlined and included a prominent role for MRI. The International Panel Criteria have since been refined, clarifying previous ambiguities.[14] With the establishment of the revised diagnostic criteria, MRI lesions in different locations can be used to meet the criteria for dissemination in space, and MRI lesions developing over time can be used to satisfy the criteria for dissemination in time (Table). In fact, the presence of multifocal brain lesions in a patient with a typical initial demyelinating event is the strongest initial predictor of progression to MS.[15,16] Imaging-based diagnostic criteria now allow for the potential diagnosis (and treatment) of MS even after a single demyelinating event, or clinically isolated syndrome. It is important to recognize that MRI characteristics need to be integrated with clinical judgment in order to accurately diagnose MS. The revised criteria place MRI in the context of clinical presentation and other paraclinical tests (ie, CSF studies). MRI alone is insufficient to make an accurate diagnosis of MS.

Table. The Updated International Criteria for Diagnosis of MS

Clinical Presentation	Additional Data Needed for MS Diagnosis	
Two or more attacks; objective clinical evidence of 2 or more lesions	None	
Two or more attacks; objective clinical evidence of 1 lesion	Dissemination in space*, demonstrated by . . .	MRI, or
		2 or more MRI lesions consistent with MS plus positive CSF, or
		Await further clinical attack implicating a different site
One attack; objective clinical evidence of 2 or more lesions	Dissemination in time†, demonstrated by . . .	MRI, or
		Second clinical attack
One attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space*, demonstrated by . . .	MRI or
		2 or more MRI lesions consistent with MS plus positive CSF
	And dissemination in time†, demonstrated by . . .	MRI, or
		Second clinical attack
Insidious neurologic progression suggestive of MS	One year of disease progression and dissemination in space*, demonstrated by two of the following . . .	≥ 9 or more T2 lesions in brain, or 4-8 T2 lesions in brain with positive visual evoked potentials
		≥ 2 T2 focal lesions in spinal cord
		Positive CSF (oligoclonal IgG bands or increased IgG index)

MS = multiple sclerosis; CSF = cerebrospinal fluid; IgG = immunoglobulinG
*For MRI lesions disseminated in space, at least 3 of the following criteria must be met: 1 gadolinium-enhancing lesion or 9 T2-hyperintense lesions in the brain and spine, at least 1 infratentorial or spine lesion, at least 1 juxtacortical lesion, and at least 3 periventricular lesions
†For MRI lesions disseminated in time, either of the following criteria must be met: gadolinium-enhancing lesion ≥ 3 months after initial presentation, but in different location from initial event; and new T2 lesion, compared with reference MRI done ≥ 30 days after onset of initial event
Modified from: 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.

The Diagnosis of MS and the Role of MRI Continued

Differential Diagnosis of MS on Imaging

White matter abnormalities (T2 lesions) on MRI are not highly specific for MS, and the differential diagnosis of cerebral lesions on MRI is broad. Although MRI is not required for the diagnosis of MS, most clinicians will employ MRI to confirm the diagnosis, stage the degree of tissue injury and ongoing inflammation, and exclude other diagnoses. The diagnosis of MS is made with the most certainty when 3 or more typical imaging findings (lesion types and aforementioned locations) are found in a classic clinical setting.[17]

Other demyelinating conditions can have an appearance that is similar to MS, but occur in different clinical settings and require different therapeutic interventions.

Acute disseminated encephalomyelitis. Acute disseminated encephalomyelitis (ADEM) is a typically monophasic demyelinating condition more common in children than in adults, which is thought to occur in reaction to vaccination or febrile illness. When compared with MS lesions, those related to ADEM tend to be larger and more symmetric (Figure 8). Although the temporal course is typically monophasic, inflammatory evolution can persist over several months. Contrast enhancement is typical in ADEM, and all lesions often enhance uniformly, underscoring their synchronous course.[18]

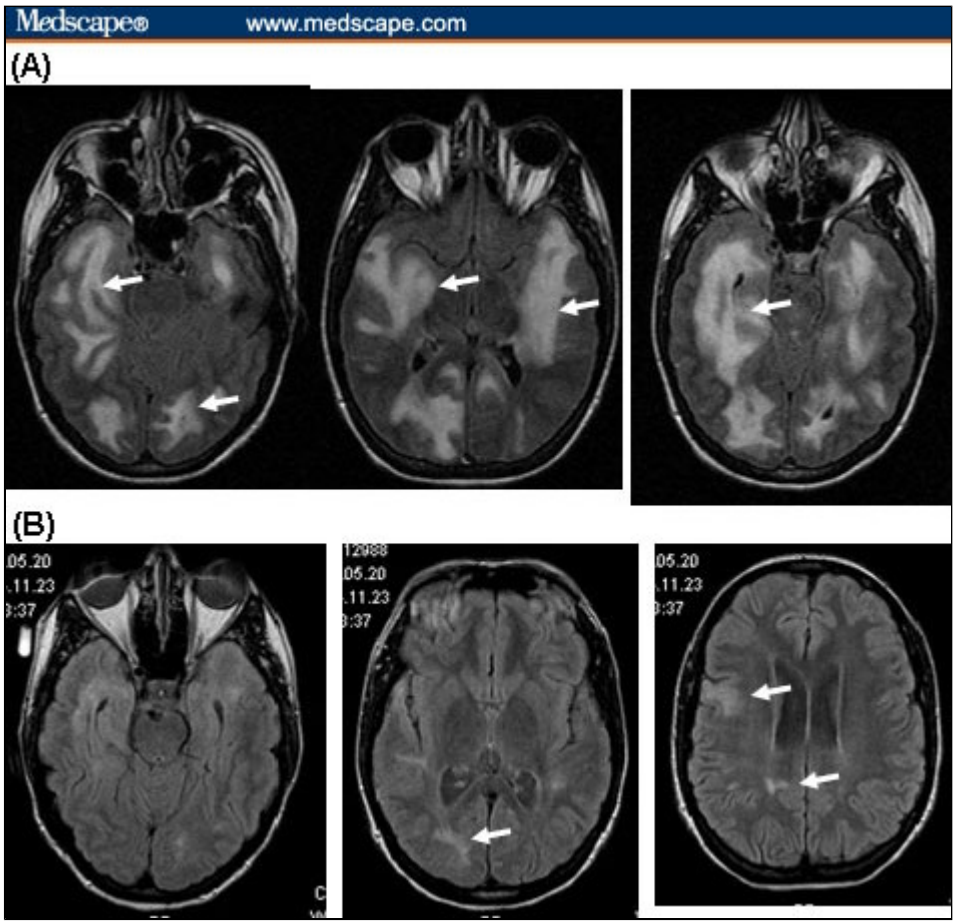

Figure 8. MRI images depicting acute disseminated encephalomyelitis. (A) FLAIR images from time of acute presentation demonstrate large, confluent areas of T2 prolongation (arrows). (B) FLAIR imaging findings almost completely normalized after a single course of intravenous (IV) steroids and IV immunoglobulin, leaving only a few, small areas of T2 prolongation (arrows).

Progressive multifocal leukoencephalopathy. Progressive multifocal leukoencephalopathy (PML) can also resemble MS on imaging in its early stages, but is clinically progressive and associated with rapidly enlarging T2 lesions that are classically nonenhancing (Figure 9).[19] Unlike the lesions of PML that relentlessly progress, individual MS lesions do not enlarge significantly over time. PML should be suspected over MS in patients who are known to have HIV/AIDS, leukemia, or are pharmacologically immunocompromised. The development of PML associated with the new MS therapy natalizumab makes differentiation on MRI characteristics alone very difficult.

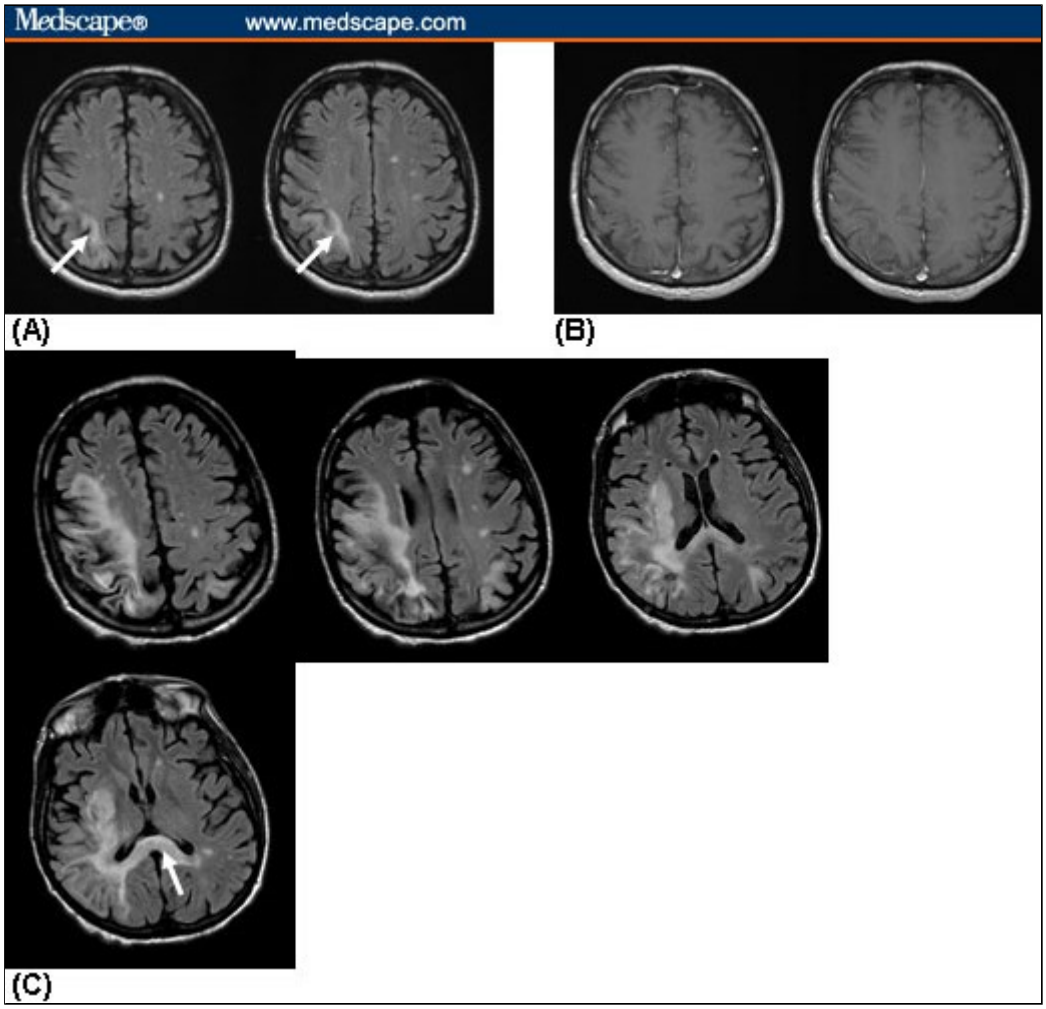

Figure 9. MRI images depicting PML. (A) FLAIR and (B) gadolinium-enhanced scans at presentation of behavior change and clumsy left hand demonstrate multifocal T2 abnormalities that do not enhance, including 1 confluent subcortical hyperintense lesion in the high right parietal region. (C) FLAIR images from 4 months later demonstrate profound enlargement of initial lesions, appearance of new lesions, and spread across the corpus callosum (arrow). Again, no lesions enhanced with gadolinium.

Vascular etiologies. Vascular etiologies can also underlie MRI T2 abnormalities and mimic MS. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is frequently considered in the differential diagnosis if there is a family history of neurologic disability. On MRI, CADASIL is identified as confluent subcortical or periventricular areas of T2 hyperintensity, which do not enhance on postcontrast T1-weighted images (Figure 10). The tendency for CADASIL lesions to evolve into T1-hypointense lesions in greater than 60% of patients can lead to the misdiagnosis of MS. Although MS has a predilection for the corpus callosum and can affect the subcortical U-fibers, CADASIL spares these areas, and more commonly affects the anterior temporal lobes.[20,21]

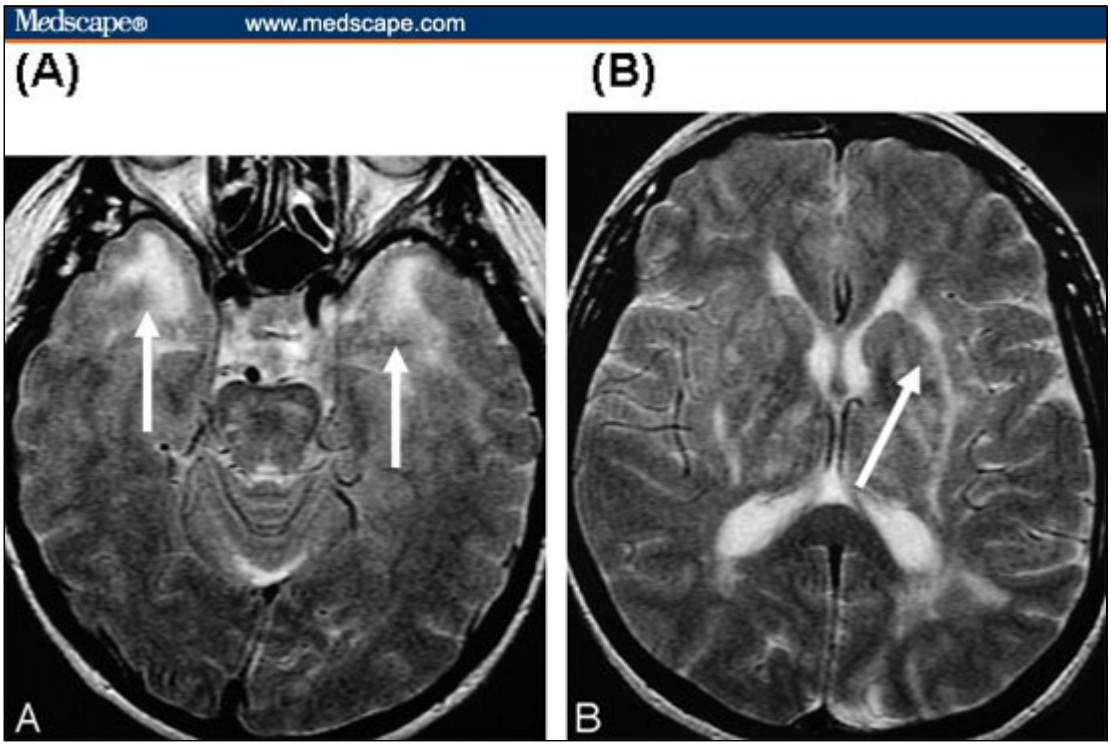

Figure 10. MRI of a patient with CADASIL, which commonly mimics MS. On these T2-weighted images, areas of increased signal in (A) the anterior temporal lobes bilaterally (arrows) and (B) external capsule (arrow) can be seen. Reproduced with permission from S Singhal, P Rich, HS Markus, The spatial distribution of MR imaging abnormalities in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and their relationship to age and clinical features, Am J Neuroradiol, Vol 26, Issue 10, pages 2481-2487, 2005, Copyright by American Society of Neuroradiology.

Subcortical leukoaraiosis represents gliosis in response to chronic deep white matter ischemia from chronic hypertension and small-vessel atherosclerosis. Its prevalence and lesion burden increase with patient age and vascular risk factors. Although at times impressive on imaging, leukoaraiosis is asymptomatic in all but the most severe cases, in which it usually presents with cognitive changes, movement disorders, or blunted affect. The lesions of leukoaraiosis tend to be located in deep white matter, and can become confluent in older or more severely affected patients (Figure 11). Small, focal areas of T2 hyperintensity that are peripherally located (ie, centrum semiovale and corona radiata) have been demonstrated in normal young patients as well as those with various neurologic and neuropsychiatric conditions. They are observed in 20% to 50% of patients with migraine in some series, and may have an underlying vascular etiology.[22] Although their smaller size and peripheral location make them theoretically easy to differentiate from MS plaques, the two are frequently confused in younger patient populations.

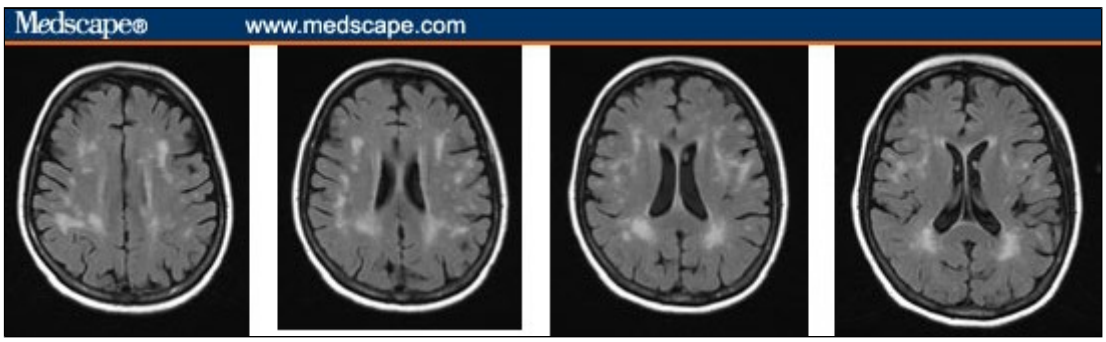

Figure 11. MRI images depicting how leukoaraiosis can be mistaken for demyelinating disease. FLAIR images from a 61-year-old woman with multiple vascular risk factors, including diabetes mellitus, hypertension, and tobacco use, who presented with unilateral paresthesias. Areas of T2 hyperintensity

are multifocal, located peripherally, and although there is a predominant lesion burden at the posterior horns of the lateral ventricles, lesions do not abut the ventricle and there is notable sparing of the corpus callosum. This patient had normal spinal fluid analysis and an atypical history for demyelinating disease.

Rheumatologic diseases. Rheumatologic diseases can at times mimic the MRI lesions of MS, with the most common considerations being systemic lupus erythematosus, Behcet's disease, sarcoidosis, Wegener's granulomatosis, and primary CNS vasculitis. These conditions are far less common than MS, and are best differentiated clinically on the basis of risk factors and other systemic manifestations. All of these conditions can result in subcortical T2 hyperintensities, unified by their vasculitic mechanism. The lesion burden is generally far lower in rheumatologic conditions than in MS, and other characteristic imaging findings of MS are absent. Specifically, T1 black holes, involvement of the corpus callosum, and large lesion burden should suggest MS, whereas other systemic symptoms combined with a low lesion burden favor another etiology.[23-26]

CNS infections. Several CNS infections can present as brain lesions on MRI. Neuroborreliosis (Lyme disease) and toxoplasmosis can appear as multifocal white matter lesions on MRI.[23,27,28]

Primary CNS neoplasms or systemic metastases. Primary CNS neoplasms or systemic metastases can create T2 hyperintensity on MRI with associated gadolinium enhancement (Figure 12). Of the primary CNS tumors, lymphoma is the only one that frequently demonstrates multifocal lesions (multiple lesions are present in over one third of cases at presentation), and therefore, sometimes enters in the differential diagnosis of MS.[29] Like MS, lymphoma commonly involves the cerebral hemispheres and corpus callosum, but lesions are often located more superficially than typical MS lesions and are clinically monophasic. In the absence of steroid treatment, the lesions of lymphoma enhance nearly universally with gadolinium. If suspected, repeated CSF cytology or brain biopsy may be necessary to positively diagnose CNS lymphoma.

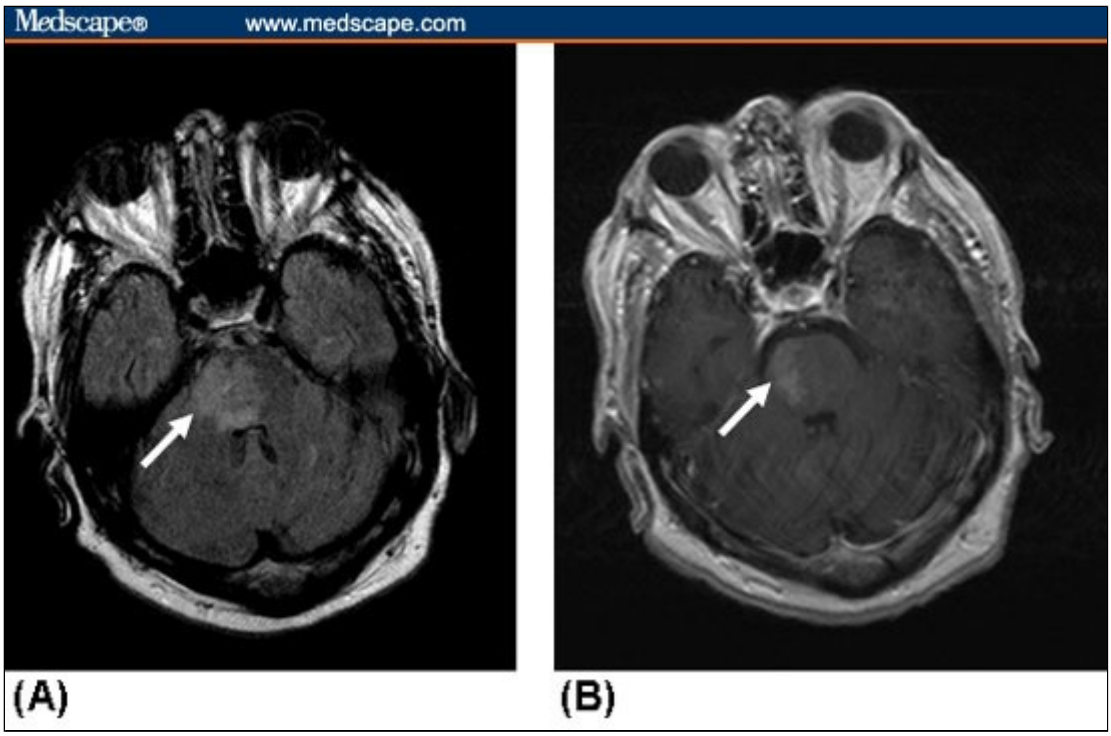

Figure 12. MRI images depicting primary CNS lymphoma. (A) FLAIR and (B) postgadolinium images demonstrated an enhancing infiltrative lesion in the mid pons. Spinal fluid cytology was positive for malignant lymphocytes.

Advanced MRI Techniques to Assess MS Disease-Related Injury and Progression

Although lesion number and location add sensitivity and specificity to the diagnosis of MS, both subclinical disease activity (measured as new lesions on MRI in the absence of signs or symptoms) and nonradiologic disease progression (clinical progression in the absence of new MRI lesions) are not uncommon. This phenomenon has become known as the "clinical-imaging paradox" of MS.[30] Furthermore, pathologic studies have clearly identified significant cortical demyelination and tissue injury, although conventional imaging studies have not demonstrated these abnormalities. These observations have led to the development of several advanced MRI measures to identify better imaging correlates of MS disease-related injury and progression.

Measurement of Brain Atrophy

Multiple large-scale studies have shown that brain atrophy is common in early relapsing-remitting MS and in some cases may be detectable as early as the first attack.[11,31,32] Atrophy of both gray and white matter occurs in MS, although the relative degrees of gray matter and white matter atrophy and the mechanisms behind each remain unknown.

Mechanistically, brain atrophy is likely the visible endpoint of irreversible tissue loss in MS, arising from multiple pathogenic mechanisms (Figure 13). MS lesion volume is partially related to whole-brain atrophy,[33-35] suggesting that atrophy may be an indirect result of MS lesions, axonal transaction,[36] and subsequent Wallerian degeneration.[37] Specific white matter atrophy may actually be underestimated in most studies, due to incomplete tissue compaction after injury.[38]

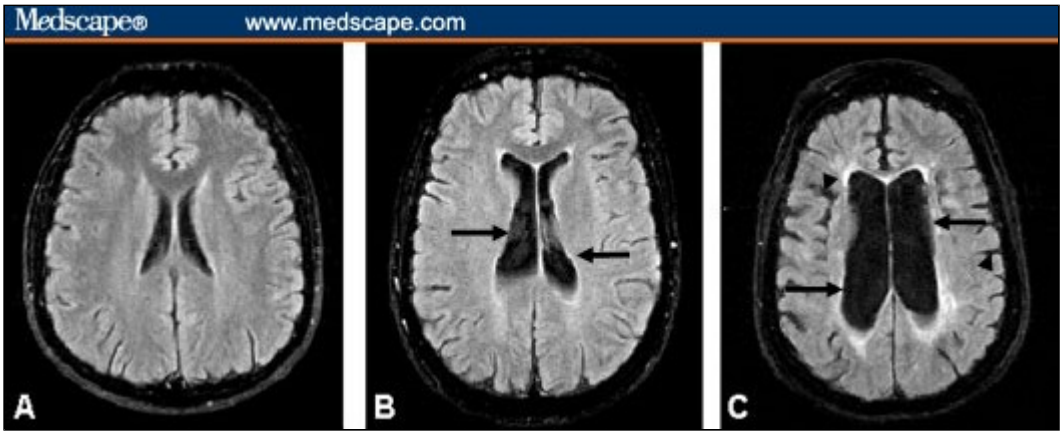

Figure 13. Brain atrophy in MS. Image A shows a healthy 31-year-old man's brain. Image B shows a 36-year-old woman who has had relapsing-remitting MS for 2 years, in which already there is cerebral atrophy as evidenced by enlargement of the lateral ventricle (arrows). Image C demonstrates severe atrophy in a 43-year-old woman who has had MS for 19 years. Atrophy can be appreciated by both severe ventricular enlargement (arrows) as well as sulcal enlargement (arrowheads).

There is a growing body of evidence that selective gray matter atrophy occurs in MS.[39-41] One study documented pathologic evidence of neuronal loss in the thalamus of patients with MS, which correlated with advanced imaging measures of reduced neuronal density.[42] Additional models of cortical atrophy in MS implicate a genetic predisposition[43] or toxic-metabolic etiologies, such as pathologic iron deposition.[44]

In vivo, brain atrophy is measured with a variety of MRI postprocessing techniques, from simple linear measures of regional or whole-brain atrophy to advanced semiautomated or automated measures of whole-brain atrophy. Linear measures, such as third ventricle width, bicaudate ratio, and brain width, can be measured without advanced computer software, have been shown to have clinical significance, and may be easy to incorporate into the longitudinal care of patients.[45,46] Many advanced 3-dimensional measures of whole-brain atrophy have been proposed, all of which fundamentally express the volume of brain parenchyma as it relates to the total intracranial volume.[9,11,47,48]

Brain atrophy is generally one of the strongest imaging correlates of physical disability.[49,50] An 8-year longitudinal study[51] found that patients with more atrophy during the first 2 years had greater disability 8 years later. At 8 years, patients with the largest amount of brain atrophy were approximately 4 times more likely to have a disability level requiring assistance with walking or worse. Thus, brain atrophy is emerging as a clinically relevant measure of MS disease progression, supported by its relationship to physical disability.

Magnetization Transfer Imaging

Magnetization transfer (MT) imaging is a method of employing free water proton interactions with their tissue environment to generate image contrast. Protons that are associated with macromolecules (such as myelin) are generally not captured by MRI. These protons do interact with and affect the spins of neighboring, free water protons, which are visualized by MRI. This interaction between macromolecular protons and adjacent water protons forms the basis of the MT contrast effect. Essentially, a baseline (usually T2-weighted) scan and a scan with identical parameters (except with an added off-resonance MT pulse) are acquired sequentially. The 2 generated images are then subtracted mathematically with a standard ratio equation to generate a third image sequence representing the MT ratio (MTR). Generally, the higher the value of the MTR in any area of tissue, the more intact that area of tissue.[52] Areas of known chronic MS lesions appear dark on MTR maps, indicating reduced tissue structure.

MTR can be applied at the level of the whole brain or in specific regions of interest. When applied to the entire brain, histograms of MTR values can be derived. A reduction in histogram peak height, overall shift of the peak height to lower values of MTR, and dispersion of the peak height have all been documented in patients with MS.[53] Furthermore, the reduction of peak height has been shown to correlate more strongly with whole-brain atrophy than does T2 lesion volume.[54] Several studies have found that white matter that appears normal on conventional imaging can have very abnormal MTR values. These abnormal areas of normal-appearing brain tissue can precede the appearance of new enhancing lesions by up to 3 months, which suggests that MTR may detect very early changes in MS injury, far earlier than breakdown of the blood-brain barrier.[55]
Most recently, MTR has been used in MS clinical trials to track response to disease-modifying therapy.[56]

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) interrogates the metabolic function and biochemistry of a small volume of tissue in vivo. An MR spectrum reveals multiple peaks representing cellular metabolic byproducts, the most easily isolated being myoinositol, choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), and lactate/lipids. Peak height or area is generally measured in relation to Cr, which remains relatively constant despite pathology. Demyelinating lesions characteristically exhibit a decreased NAA:Cr ratio and an increased Cho:Cr ratio (Figure 14).[57,58] Like MT imaging, MRS has also identified abnormalities within brain tissue that appears normal on conventional imaging, again exposing the diffuse pathology of MS and tissue changes in advance of overt lesion development.[59-61] Newer MRS techniques aim to resolve other metabolic peaks, such as glutamate, to further differentiate changes of inflammation and demyelination from those of potential benefit, such as remyelination.[62]

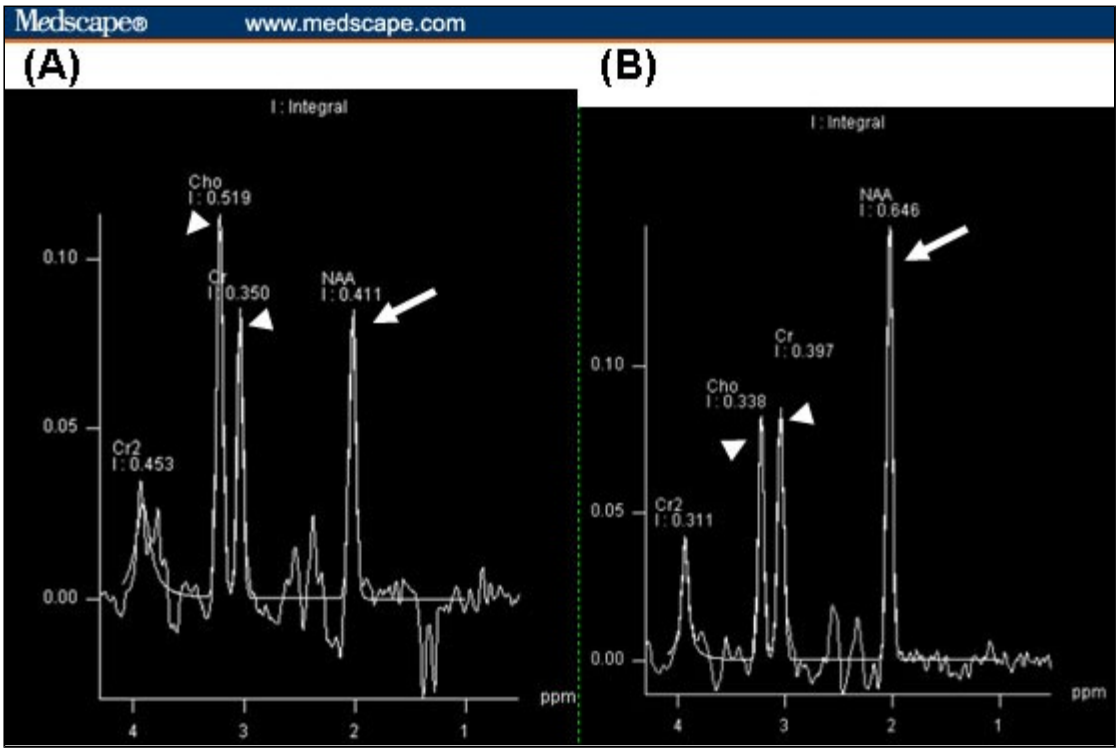

Figure 14. MRS of (A) a demyelinating lesion compared with (B) normal contralateral white matter. Spectroscopic peaks quantify the amount of different cellular molecules within tissues. By comparing the NAA, Cr, and Cho peaks, a decreased NAA:Cr ratio (arrows), indicating neuronal dysfunction and axon loss, and an increased Cho:Cr ratio (arrowheads), indicating increased cell-membrane turnover, can be appreciated. The altered ratios are characteristic of the pathology seen in MS.

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is the most recently evolved imaging measure of axonal and myelin integrity. By measuring the 3-dimensional restriction of the free water molecules, DTI yields indirect information about the relative size, shape, and orientation of tissue fibers. DTI is an ideal technique for evaluating the integrity and direction of white matter fiber tracts in the brain. DTI can be used to measure the overall amount of diffusion (mean diffusivity) and the degree of orientation of water diffusion, or anisotropy (fractional anisotropy) (Figure 15). As an example, a brain region containing predominantly cell bodies (eg, cortex) would have higher mean diffusivity and lower fractional anisotropy than a voxel containing tightly packed bundles of fiber tracts oriented parallel to one another (eg, corpus callosum). Like other advanced imaging methods, DTI has been shown to demonstrate diffuse damage in normal-appearing brain tissue.[63-65] Also, DTI of MS lesions is able to differentiate those lesions with severe underlying tissue damage (ie, T1 holes).[66] DTI measures of axonal disruption in the optic nerve of patients recovering from optic neuritis correlate with the degree of functional recovery.[67] Most impressively, DTI is used to perform "fiber tracking," which is able to generate 3-dimensional images of selected axonal tracts. Fiber tracking allows interrogation of individual functional pathways within the brain or cervical spinal cord, evaluating the remote response to a demyelinating lesion.[68,69]

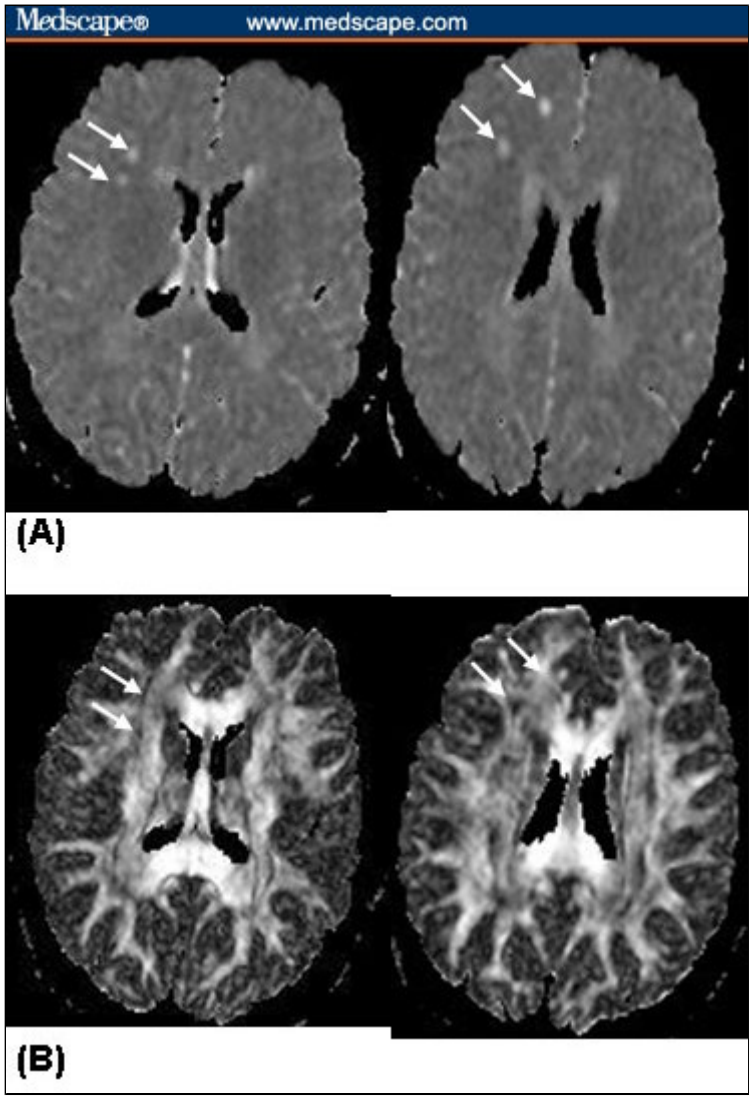

Figure 15. DTI in MS. DTI images of (A) mean diffusivity demonstrate increased diffusivity in MS lesions (arrows), whereas images of (B) fractional anisotropy demonstrate decreased anisotropy in the same region (arrows). Both images indicate areas of tissue injury.

The Role of MRI in Patient Management of MS Disease

Although multiple studies have established the importance of MRI in the diagnosis of MS and highlighted its ability to detect the effect of treatment across large numbers of patients, the proper utilization of MRI to manage an individual patient's disease remains debated. Questions that are commonly encountered include: What is the yield of reimaging a patient in the midst of a clinical relapse? What is the significance of new lesion appearance in the absence of a clinical relapse? Should treatment be altered or initiated on the basis of imaging findings alone? Although precise answers to these questions are not known, evidence from large trials of MS therapeutics guide individual treatment decisions, and recommendations of a large commissioned task force have been published to address these issues.[70]

A correlation between T2 lesion burden and physical disability in most clinical trials (although moderate in degree statistically) suggests that the appearance of new T2 lesions (Figure 16) does have clinical relevance. Especially in light of recent evidence that early development of new T2 lesions predicts long-term disability,[33] surveillance MRI to ensure adequacy of treatment (especially in the first few years after diagnosis) is now advocated by some clinicians. Guidelines have been established to guide clinicians' use of MRI for monitoring in the longitudinal care of patients.[70] Most clinicians will obtain a surveillance brain MRI 1 year after beginning disease-modifying therapy, to complement the clinical assessment in ensuring adequate response to therapy. Brain imaging is sufficient, as spine lesions in MS are more likely to be symptomatic, and therefore, rarely occur without clinical equivalent. Once a patient has been stable for a number of years and his or her response to therapy established, imaging is reserved for episodes of relapse when a treatment failure is suspected. The appearance of new T2 lesions or gadolinium-enhancing lesions on either surveillance MRI or in association with a clinical relapse may be signs of inadequate response to treatment.[71] An inadequate treatment response may be due to medication noncompliance, neutralizing antibodies to interferon therapy, or aggressive disease activity requiring therapeutic escalation. In later stages of the disease, such as secondary progressive MS in which disability often slowly progresses in the absence of new T2 or enhancing lesion formation, routine imaging has lower utility.

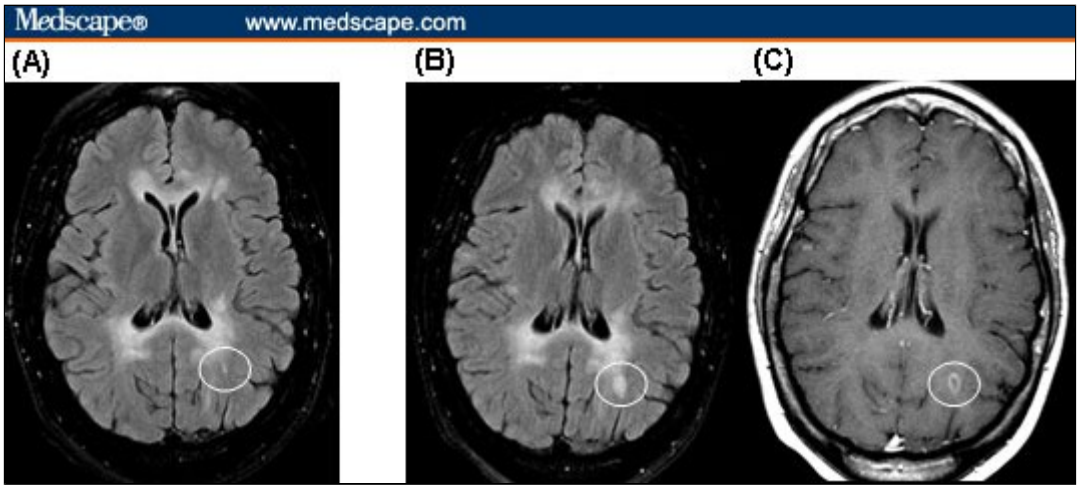

Figure 16. Using MRI to follow patients over time. The scan depicted in (A) was acquired 4 months prior to the scans shown in (B) and (C). Even in a patient with large, confluent MS lesion burden (A), the appearance of a new lesion on FLAIR (B), especially with associated gadolinium enhancement (C), is a sign of ongoing disease activity.

The Role of MRI in Assessing the Effects of Therapy

Preventing the development of new T2 lesions appears to be a logical therapeutic goal in MS patients. Gadolinium-enhancing lesions and T2 lesions are associated with long-term development of clinical disability and brain atrophy.[33] Indeed, all 6 FDA-approved therapies have demonstrated robust efficacy on MRI measures of disease activity. Glatiramer acetate is associated with a 30% reduction in gadolinium-enhancing and T2 lesions, whereas beta-interferons are associated with approximately 70% reduction in T2 lesions.[72-74] Surprisingly, despite the differences in MRI outcomes between glatiramer acetate and interferon therapies in the phase 3 clinical trials, all of these trials observed a relatively similar one third reduction in clinical relapses, suggesting that the beneficial effects of MS therapies are not completely captured by MRI. Furthermore, the discordance between MRI and clinical efficacies with the interferon therapies has been observed with many other therapies, and the explanation for this discordance remains unknown.

Phase 3 trials of mitoxantrone found an 85% reduction in T2 lesions,[75] whereas studies of natalizumab found a 92% reduction in gadolinium-enhancing lesions and an 83% reduction in T2 lesions.[76]

The relative greater frequency of MRI lesions compared with clinical relapses (typically about 5:1) has led to the use of MRI as the primary outcome of most phase 2 clinical trials in MS. After demonstrating efficacy in the preliminary phase 2 trials, MRI measures usually become secondary outcomes in subsequent definitive phase 3 clinical trials. MRI outcomes become important supporting evidence for the eventual licensing of MS therapies.

MRI is also useful in managing patients currently receiving therapy and is integrated along with clinical assessments when deciding to change therapy. New T2 lesions while on beta-interferon therapy have greater specificity in predicting future progressive disability and atrophy than clinical measures (ie, relapse rate).[71] The appearance of new MRI lesions while on beta-interferon may necessitate a change or escalation of treatment strategy.

There are several limitations in MRI assessment of MS therapies. The greatest limitation is the limited, modest correlation between MRI measures and disability.[77] This dissociation likely arises due to a combination of the insensitivity of clinical measures as well as the plasticity and regenerative potential of the brain (making no measurable impact on clinical performance despite many lesions). This discordance between clinical and imaging measures limits the surrogacy of MRI and prevents it from being a primary outcome in definitive licensing trials. This discordance is even greater in secondary progressive MS, in which progressive disability appears to be almost completely independent of new MRI lesions and the impact of MS therapies of the development of new MRI lesions.[78-81]

Advanced MRI techniques hold promise for addressing the limitations inherent in conventional MRI assessment of MS therapies. Advanced MRI techniques more sensitively characterize tissue integrity, and so provide a broader dynamic range of pathology than conventional MRI. Brain atrophy has already been successful when applied to clinical trials in relapsing-remitting MS.[11,47,82] Studies are under way to evaluate the potential utility of DTI and MTR in assessing tissue recovery after inflammation and potential impact of MS therapies.

Conclusion

MRI is a powerful tool in the diagnosis of MS, including the differential diagnosis. MS lesions have certain characteristics that when recognized, can help in the accurate diagnosis of MS. Understanding of both MS inflammation and MS neurodegeneration has greatly improved through MRI. Advanced MRI methodologies, such as MT and DTI provide further insight into tissue integrity and its disruption in MS. MRI is also helpful in assessing the effect of MS therapies, both in clinical trials and routine practice. Future application of advanced MRI methods to MS therapies will help further our understanding of degeneration and potential neuroprotective therapies.

Measuring Educational Impact

Case #1: A 30-year-old woman presents to the office for evaluation of visual changes and dizziness. She states that she began seeing double approximately 5 days ago and noticed that she was having unsteadiness with walking. She had similar complaints 3 months ago, which spontaneously resolved on their own after a few days. She is otherwise healthy and is taking no medications. Physical exam reveals unsteady gait. She also exhibits some weakness in the lower extremities and brisk tendon reflexes. The physician recommends MRI of the brain to evaluate for the possible diagnosis of MS.

8. Which of the following advanced imaging modalities can detect very early changes in MS injury that may appear normal on conventional MRI imaging?

- MTR
- CT scan with contrast
- PET scanning
- Ultrasonography

9. Which of the following imaging correlates is the strongest predictor of physical disability?

- Size of lesions on T2 images
- Enhancement of lesions on T1 images
- Brain atrophy
- Number of T2 lesions

Case #2

A 26-year-old man presented to his sports medicine physician 9 months ago for evaluation of his left leg feeling weak. Subsequent evaluation was unable to confirm any specific diagnosis. Recently, he began to lose feeling in both of his legs, experience tingling in his left hand, and complain of visual problems. Physical exam reveals a subtle weakness with muscle testing in the lower extremities. He has decreased sensation to light touch and pinprick as well as vibration in both feet. Extensive laboratory evaluation is normal except for the presence of oligoclonal bands in the cerebrospinal fluid. Subsequent MRI imaging of the brain reveals 3 lesions in the white matter that were hyperintense on T2-weighted images, and isointense on T1-weighted images, and are nonenhancing on postcontrast images.

11. In addition to MS, which of the following would be your next differential diagnosis?

- PML
- Lupus cerebritis (systemic lupus erythematosus)
- Subacute combined degeneration
- CNS lymphoma

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