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CLINICIAN'S PRIMER ON MULTIPLE SCLEROSIS

Basic Course on MRI

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Basic Course on MRI 2

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TARGET AUDIENCE

This activity is intended for neurologists, primary care physicians, MS nurses, fellows, residents, and other health care professionals actively involved in the care of patients with MS.

ACTIVITY DESCRIPTION

Multiple sclerosis (MS) is progressive disease of the central nervous system (CNS), affecting approximately 400,000 people in the United States. Magnetic resonance imaging (MRI) has become an important diagnostic and monitoring tool in MS since its introduction in the 1980s. It facilitates a more rapid and accurate diagnosis of MS, provides techniques to monitor responses to MS-targeted therapies, and aids clinicians in making better management decisions. MRI-derived measures now are utilized routinely as secondary outcome markers in clinical trials assessing new therapies for MS.

The Clinician's Primer on Multiple Sclerosis: Basic Course on MRI is a reference source on the practical and optimal use of MRI in the clinical setting. It provides the most current information based on collective expert guidelines, clinical literature, and recommendations from the Consortium of Multiple Sclerosis Centers (CMSC). Basic MRI concepts as they apply to MS, as well as some of the more advanced MRI methods are discussed. Subsequent to providing initial learning opportunities, the Clinician's Primer is intended to serve as a continuing resource for clinicians, enabling continual improvement of patient care.

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe MR imaging protocol as presented in the most recent CMSC guideline
- Describe how MRI is used to find spinal cord and brain lesions in MS
- Explain the differences between T1-weighted and T2-weighted images
- Discuss how gadolinium is used in MRI, as well as its risks

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Chris S. Conner, PharmD	No financial relationships to disclose

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A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better. Your statement of credit will be mailed to you within 4-6 weeks.

1 INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated, progressive disease of the central nervous system (CNS) characterized by multifocal and widespread demyelination and axonal loss.[1-4] Approximately 400,000 people in the United States have MS, with over 2.5 million cases worldwide. MS is classified into subtypes according to the presence or absence of acute attacks of new neurologic symptoms, the ability of the CNS to recover from damage, and whether the accumulation of clinically evident damage appears to proceed in the absence of identified relapses. A brief review of these subtypes and their clinical course is presented in **Table 1**. Since its introduction in the 1980s, magnetic resonance imaging (MRI) has emerged as an indispensable diagnostic and monitoring tool in MS. In addition to contributing to a more rapid and accurate diagnosis of MS, it has enabled clinicians and researchers to visualize the pathologic process of the disease and how it changes over time, evaluate ongoing clinical status of patients, monitor response to MS-targeted therapies, and make better management decisions. Furthermore, conventional MRI (cMRI)-derived measures are accepted routinely as secondary outcome markers in many clinical trials assessing new therapeutic modalities for MS.[2,5] While MRI surrogates are not yet substitute markers for clinical outcomes,[6] analyses suggest that they may eventually accumulate adequate support for acceptance.[7]

The clinical literature on MS is voluminous, making it time consuming for neurologists and other practitioners to stay abreast on recent developments, guidelines, and protocols pertaining to the use of MRI. This is particularly problematic for those who do not focus their practice solely on MS.

The role of MRI in the diagnosis of MS is now well incorporated into modern diagnostic criteria.[8] Nevertheless, using MRI as a tool for monitoring disease progression, treatment response, and prognosis is less well defined, especially after first clinical presentation; it has been left to clinicians' judgment to determine how to best utilize MRI in MS care.[5,9] Recently, the use of MRI in the diagnosis of MS in patients with a clinically isolated syndrome (CIS) has been better defined by the **Magn**etic **I**maging in **MS** (MAGNIMS) criteria, and numerous imaging studies are providing a framework for the role of MRI in clinical practice. While the role of cMRI still is being optimized, even newer and more advanced MRI methods are under development or becoming available to clinicians. Technologies, such as magnetization transfer imaging (MTI) and magnetic resonance spectroscopy (MRS), promise to offer improved understanding of MS. Determining which MRI techniques should be used, how, when, and how often

TABLE 1: Forms of MS and Clinical Course

Relapsing-Remitting MS (RRMS)	• Most frequent form – 80%-85% of patients • Female preponderance of about 2:1, with the ratio likely increasing over time • Onset announced by a clinically isolated syndrome (CIS) such as optic neuritis • Characterized by acute episodes of neurologic dysfunction evolving over several days and peaking after 1-2 weeks, then stabilizing and improving spontaneously or in response to corticosteroids over several weeks or even months • Recovery from relapse episodes may be only partial in some patients with residual symptoms persisting indefinitely, especially sensory symptoms • Any residual deficits must be stable between attacks
Secondary Progressive MS (SPMS)	• After 10 or even 20 years of RRMS, relapses become less frequent and many patients transition into SPMS, an insidious and progressive deterioration of neurologic function • Progression of neurologic compromise in SPMS must occur independent of discrete recognized relapses and be evident between clinical attacks
Primary Progressive MS (PPMS)	• Occurs in about 10% of patients • Characterized by steady deterioration of neurologic function from disease onset in the absence of prior attacks or in slowly evolving relapses • Frequency of occurrence similar in men and women
Progressive Relapsing MS (PRMS)	• Much rarer form of MS • Begins as PPMS but over time is associated with occasional relapses superimposed on the continuous disease progression

can be confusing and challenging for clinicians. Unfortunately, there is evidence of suboptimal application of MRI techniques in the management of MS patients in everyday clinical practice.[10]

This Primer offers clinicians who diagnose and treat MS a reference source on the practical and optimal use of MRI in the clinical setting. The *Clinician's Primer on MS: Basic Course on MRI* provides this information based on relevant data from clinical literature, collective guidelines from experts in MS, and practical recommendations from the Consortium of Multiple Sclerosis Centers (CMSC).[11,12] A review of basic MRI concepts as they apply to MS and the dynamic pathology of MS seen on MRI are presented initially to lay the foundation for the practical clinical use of MRI techniques. Some of the more advanced (nonconventional) MRI methods also are discussed.

2 MRI IN MS: General Concepts

BASICS OF MRI TECHNOLOGY

MR images are generated by signals derived from protons (hydrogen nuclei) in water following the application of radio-frequency (RF) pulses in the presence of a strong magnetic field.[5,13-16] The magnetic field of a 1.5 Tesla (T) magnet in MRI scanners is about 30,000 times stronger than the magnetic field of the earth.[13] Hydrogen nuclei, which act as tiny molecular magnets, align with the external field within body tissues and create a net magnetization within the body.

Energy in the form of RF pulse sequence is applied via copper coils in the scanner, exciting and perturbing the hydrogen nuclei, which then relax and realign to their previous state of equilibrium. This realignment emits energy as an RF signal, or spin echo, which is analyzed by another set of coils.[13,17,18] The RF off-and-on cycling repeats several hundred times per minute to create high-quality images and results in the repetitive and loud vibration noise during the procedure.

The signal intensity from different tissues is dependent on proton density (PD; the concentration of tissue protons in the form of water and macromolecules, such as fat) and the rate at which nuclear MR signals decay in the magnetic field after the RF pulse.[5,18] The time required for protons to realign within the magnetic field and give up the RF energy that perturbed their alignment is known as the T1 relaxation time (longitudinal relaxation). Protons absorbing energy from an RF pulse all are initially in phase alignment, and the time for protons to lose their phase alignment within the original magnetic field is the T2 relaxation time (transverse relaxation). T2 relaxation occurs by an exchange of protons in high- and low-energy states without a loss of energy to the molecular environment. T2 time is always shorter than T1 time. The PD, T1 relaxation time, and T2 relaxation times can be manipulated to determine the appearance of tissues on the MR image.[5]

Image Characteristics

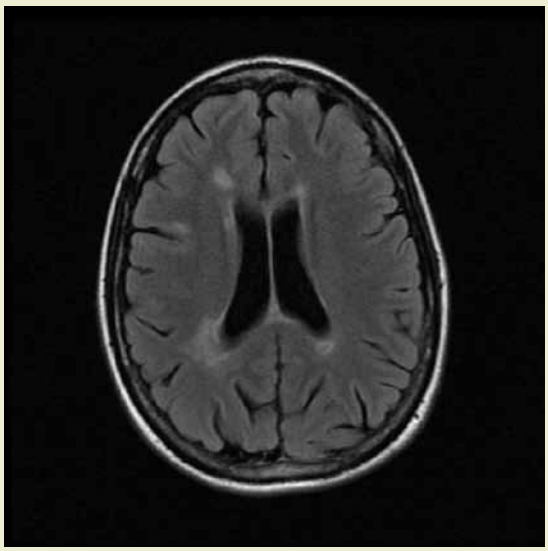
Image characteristics can be altered by changing pulse-sequence parameters. The most important parameters are the repetition time (TR) and echo time (TE).[18] TR represents the time between consecutive 90-degree RF pulses, and TE is the time between the initial 90-degree RF pulse and the echo.[18] The most common type of pulse sequence is the spin echo (SE) sequence, with pulse timing adjusted to generate T1-weighted, proton density, or T2-weighted images.[18-20] PD and T2-weighted images are generated with long TRs. With a short TE, image appearance is determined primarily by PD, and with a long TE, the T2 effect is emphasized.[5] T1-weighted images usually are generated at a short TR and TE.[5] Dual echo (or multi-echo) sequences can be employed to simultaneously obtain both PD and T2-weighted images.[19]

In T2-weighted images, areas of pathology often reflect increases in water content or edema; however, these changes are nonspecific and may be related to various abnormalities.[3,21] Gadolinium (Gd)-containing contrast agents with T1-weighted images show increased signals from brain tissue where the blood-brain barrier (BBB) is compromised.[5,22]

Fluid-Attenuated Inversion Recovery (FLAIR) Imaging

FLAIR imaging is used commonly in patients with MS or suspected MS. FLAIR uses a special inversion pulse with a long TE, which generates heavy T2-weighted images and nulls (water appears dark instead of bright on T2-weighted scans)

FIGURE 1: FLAIR Imaging



FLAIR image of a patient with MS showing periventricular and white matter lesions.

the cerebrospinal fluid (CSF) signal (**Figure 1**).[5,20] This technique enhances MS-lesion conspicuity, especially for lesions occurring at the brain and CSF interface.[20] T1 values of white matter (WM), gray matter (GM), and CSF differ; therefore, single- and double-inversion pulses also may be applied to selectively null one or more of these tissue types.[5]

The inversion pulse also can be combined with a fast spin echo (FSE) pulse sequence (which acquires multiple echoes per TR).[20] This technique, known as fast FLAIR, can perform imaging of 36 slices of 5 mm tissue thickness in about 5 minutes; it provides increased lesion conspicuity and lesion-to-CSF contrast compared with conventional SE imaging.[20]

CONVENTIONAL MRI TECHNIQUES IN MS

As early as the 1800s, postmortem studies characterized the pathology of MS lesions (plaques).[23] However, it was not possible to assess and quantify these lesions in vivo until the introduction of MRI in the early 1980s.[24] A seminal study by Young and associates[25] over 25 years ago demonstrated the sensitivity of MRI in detecting MS-related CNS damage. Other studies subsequently confirmed that areas of T2-signal abnormalities on MRI corresponded to the MS lesions seen in postmortem examinations[23,26] and that the size of acute lesions on MRI tended to change over time.[27] Further studies showed that some MRI lesions were enhanced after administration of Gd-containing contrast material and that this enhancement was related to inflammation and increased permeability of the BBB.[23,28] In the early 1990s, it was shown that enhancing lesions occurred 5-10 times more frequently than clinical relapses in MS patients.[23]

Collectively, these data laid the foundation for cMRI to assess CNS pathology, contribute to the diagnosis of the disease, and help physicians monitor MS-related CNS tissue changes over time. An exact description of what constitutes cMRI continues to evolve. However, a suggested practical definition for cMRI could be "approaches enabling reconstruction of images for real-time viewing, which can be interpreted subjectively by an experienced clinician without the need for extensive offline data transformation, processing, or analysis."[5] Most experts agree that Gd-enhanced T1 images, T2-weighted images, and noncontrast T1-weighted images comprise conventional techniques that at least partially fulfill this definition. By comparison, nonconventional techniques (discussed below) include advanced pulse sequences, beyond the basic pulses performed for T1 and T2, and typically require post-processing to analyze and display data. They may offer other imaging information as well, such as functional assessment of neuronal metabolism and viability or diffusion properties of water.

Some advantages and limitations of the 3 cMRI methods are shown in **Table 2** (page 8).[9,21,29-31] These techniques enable clinicians to assess MS lesions over time. However, one of the main limitations of cMRI is that clinical changes in MS are not consistently related to MRI changes.

Measuring brain atrophy—typically thought of as a nonconventional technique—is considered an additional cMRI method by some investigators.[21] Yet, while estimates of atrophy can be derived from conventional images, appreciation of the ~1% annual rate of brain atrophy that typifies untreated MS requires substantial image processing and manipulation of sequential images to obtain reproducible quantitative measures of this amount of global tissue loss. In contrast with lesion measurement, brain atrophy reflects the end result of severely damaging pathological processes seen both focally (lesions) and diffusely (otherwise normal-

TABLE 2: Features of Conventional MRI[9,21,29-31]

Technique/Advantages	Limitations
T2-Weighted Images • Highly sensitive for detection of MS lesions • Useful for diagnosis of MS • Useful for monitoring by counting new or enlarged lesions visible on monthly scans • FLAIR particularly effective for maximizing contrast between deep gray-matter lesions and normal tissue • Useful for assessing overall disease burden (eg, measuring total hyperintense lesion volume on annual scan)	• Poor correlation with clinical status (ie, clinical disability vs rate of accumulation of T2-hyperintense lesions) • T2 hyperintensities cannot distinguish specific pathological processes, such as inflammation, edema, demyelination, Wallerian degeneration, axonal loss • Normal-appearing white matter (NAWM) or normal-appearing gray matter (NAGM) may exhibit pathologic changes (eg, structural, biochemical) not visualized on conventional T2 imaging • Inconsistent physical positioning of the patient in the magnet, or prescription of slice location and orientation, can lead to difficulties or frank misinterpretation of change over time
Gd-Enhanced T1 Images • Identifies current or recently active lesions (distinguishes from inactive lesions) • Enhancement correlates with breakdown of the BBB and active inflammation	• Does not provide information on tissue damage or extent/severity of inflammatory activity • Often correlates poorly with concurrent clinical disease activity, especially when obtained at predefined intervals
Noncontrast T1-Weighted Images • Reveals chronically hypointense lesions or black holes, representing areas of severe demyelination and axonal loss • Chronic T1 hypointensities have correlated better with clinical disease severity than T2-weighted imaging	• Definition of "black holes" is arbitrary • T1-hypointense lesion volume does not provide information on intrinsic pathology of individual lesions or pathology outside of lesions • Inconsistent physical positioning of the patient in the magnet, or prescription of slice location and orientation, can lead to difficulties or frank misinterpretation of change over time

appearing brain tissue) and correlates better with clinical status.[32] For purposes of this primer, T1- and T2-weighted imaging and their variants are considered cMRI techniques. Brain atrophy measurement is considered a nonconventional technique.

Most commonly, for the patient with MS or suspected MS, cMRI consists of several series of acquisitions based on available pulse sequences that enable optimal tissue contrast for lesion detection.[3,5] Currently recommended clinical protocols include FLAIR, axial and especially sagittal, axial dual-echo or single-echo T2-weighted images, and pre- and post-Gd-enhanced axial spin-echo T1-weighted images.[3,5,11] Post-Gd T1 imaging is important particularly if suspicious lesions are seen on FLAIR in the patient with suspected MS.[5] Brain atrophy assessment via 3 dimensional (3D) T1 is considered an option.[11]

Comparison With Computed Tomography (CT)

Both CT and MRI are computer-based imaging techniques that display areas of the body under examination in thin tomographic slices. However, as previously discussed, MRI does not share the need for the ionizing radiation required in CT.[13] Thus, MRI is inherently safer than CT and usually provides better images of soft tissue. With regard to clinical use, MRI is more sensitive than CT for evaluating brain and spinal cord pathology in general and for detecting demyelinating MS lesions. Earlier diagnosis of MS can be achieved using MRI due to greater and more accurate lesion identification.[33-35]

In one early study involving 102 subjects (82 with diagnosed or suspected MS and 20 controls), MRI (0.15 T, T2 weighted) was consistently superior to both regular-contrast and high-volume delayed (HVD) CT in detecting MS lesions.[35] Lesion detection was made by MRI evaluation in 97% of patients with chronic, previously well-documented, stable MS compared with 54% of patients in this group upon subsequent evaluation with HVD CT. In the same study, 88% of patients who were suspected of and ultimately diagnosed with MS by a neurologist were identified as having lesions by MRI compared with 52% by contrast or HVD CT.

TABLE 3: Features of Some Nonconventional MRI Techniques[2,3,21,22,36,37]

Brain Atrophy Measurement	• Biomarker of disease process • Assesses extent of tissue loss • Significant correlation with disability, superior to that of lesion measures • Moderate predictive value for development of subsequent neurological impairment • Limitation of insensitivity to disease changes • Can be sensitive to the patient's hydration status and the recent use of some drugs like methylprednisolone
Magnetization Transfer Imaging (MTI)	• Based on interactions between protons in free water pools and those bound to macromolecules • Measures tissue damage, as seen by a decrease in the magnetization transfer ratio • Quantifies pathologic changes in normal-appearing tissues undetectable on cMRI • Sensitive method to detect disease activity and monitor disease progression
Magnetic Resonance Spectroscopy (MRS)	• Quantitative measure of neurometabolites that reflect tissue changes, such as demyelination or remyelination, loss of axonal/neuronal integrity, and gliosis • Decreases in N-acetylaspartate (NAA) suggest axonal injury • Elevated peaks of lactate indicate inflammation • Elevated peaks of choline, lipid, and other macromolecules suggest demyelination/remyelination • Elevated peaks of myo-inositol suggest gliosis • Identifies abnormalities in NAWM • Decrease in ratio of NAA:creatine has correlated with disability and cognitive dysfunction
Functional MRI (fMRI)	• Detects changes in blood oxygen levels • Identifies abnormal patterns of brain activation • Can assess CNS damage and adaptive functional changes associated with movement or motor learning
Diffusion Tensor Imaging (DTI)	• Measures the magnitude and directionality of water diffusion • Provides information on the orientation, integrity, size, and geometry to neural tracts in CNS • Assesses occult and progressive tissue damage in NAWM and normal-appearing GM

NONCONVENTIONAL (ADVANCED) MRI TECHNIQUES IN MS

The importance of neurodegeneration and axon injury in the pathology of MS has been emphasized in recent research. Thus, there is a need to develop more advanced imaging techniques to measure CNS inflammation and the consequence of disease progression over the long term.[36] Much of the focus now in MS literature is on newer and more advanced MRI methods, such as MTI, MRS, and precise measurements of brain and spinal cord atrophy.[2,5,36] Features of these technologies are highlighted in **Table 3**.[2,3,21,22,36,37] Advanced methods can provide greater insight into understanding the pathogenesis of MS, offer greater discriminatory power to glean more useful diagnostic and monitoring information, and add additional information to the anatomic definition provided by cMRI.[2] However, the "limitations" of cMRI must be placed into perspective. Without the useful anatomic data provided by conventional imaging, advanced methods also would be quite limited.

Although nonconventional techniques often are available on modern MR scanners, they are not used widely in the routine clinical setting for the diagnosis and management of MS patients. Further, nonconventional techniques may require more expertise to perform and interpret correctly, are often more susceptible to motion issues and scanner artifacts and may take longer to acquire than cMRI techniques. Guidelines for the use of these techniques have not been met with consensus in neurology and neuroradiology circles. However, nonconventional MRI techniques undoubtedly will play a major role in the future but, at present, are available primarily for use in a few select centers and in research.

SELECTION OF MRI TECHNIQUES FOR CLINICAL USE IN MS

Readily accessible to the practitioner, cMRI techniques provide insight into multiple aspects of disease extent and severity, which are useful on a daily basis in the clinic and serve as the cornerstone of MRI-based outcomes in MS clinical trials.[30] Owing to its availability and proven accuracy, cMRI remains the method of choice for helping to diagnose MS. When used appropriately, it also is highly satisfactory for monitoring disease severity and response to treatment.[21,30] The potential limitations of cMRI methods can be minimized by optimal use and adherence to recommended protocols in

terms of imaging techniques, frequency of imaging, and use and application of imaging findings in clinical practice.[12,38]

The use of cMRI to view MS pathology and evolution, as well as its role in the diagnosis and assessment of clinical status/disability in MS patients over time is discussed further. Applications of some nonconventional MRI techniques will be addressed subsequently.

3 MS PATHOLOGY & ITS EVOLUTION THROUGH THE EYES OF CONVENTIONAL MRI

BASICS OF MS LESIONS

Conventional MRI and histopathological analysis have shown that MS lesions can occur anywhere in the CNS, including GM, but most commonly they occur in deep WM and the spinal cord. At fresh brain dissection, the typical MS plaque is gray or pink and < 5-10 mm in diameter. It is characterized histologically by inflammation, demyelination, astrocyte proliferation with ensuing gliosis, and axonal degeneration.[39] During the evolution of MS lesions, an accumulation of lipid-laden macrophages containing myelin is evident, and axons traversing the plaque exhibit marked irregular beading.[1,39] Present initially, oligodendrocytes are lost as gliosis progresses.[39] Four distinct patterns of pathology have been described, although whether these patterns represent distinct subsets of disease or different stages of lesion evolution is not known.

Preferential lesion sites in MS include the periventricular WM, corpus callosum, brainstem, subcortical region, U-fibers, optic nerve and tracts, juxtacortical gray-white matter, and cervical spinal cord.[2,3,39] Lesions in the brainstem, cerebellum, spinal cord, or optic nerve commonly are associated with sensory or motor deficits, changes in balance, and optic neuritis or other ocular symptoms, such as diplopia or nystagmus.

GM and cortical pathology in MS only recently have been investigated thoroughly. Pathological studies have shown that cortical demyelinating lesions are prevalent and widespread; primarily affect the subpial layers of the cerebral cortex; and are difficult to visualize and therefore are greatly underreported. These lesions likely are associated with motor, sensory, and cognitive disability and may cause axonal and dendritic transection and neural loss via apoptosis.[5,29,40-43]

On neuropathological analysis, many if not most cortical lesions also involve cortical WM.[29] Cortical-lesion evolution has been difficult to detect with cMRI, except for those adjacent to a WM component (eg, juxtacortical). Nevertheless, increased appreciation of purely intracortical lesions has been reported recently with cMRI techniques.[44,45]

Precise mechanisms leading to lesion formation in MS are unclear, although there is good evidence to support genetic and environmental influence in triggering an autoimmune process.[1,39] Postmortem studies and animal models suggest that perivascular inflammation with alteration of the BBB integrity and permeability is a key event in lesion pathogenesis.[29,34] Disruption of the BBB is evident at sites of inflammation in acute lesions; however, the vessel wall is preserved, distinguishing MS lesions from vasculitis.[39] During the initial inflammatory phase of the disease, autoreactive lymphocytes are activated in the periphery and traverse vessel walls in the BBB to enter the CNS, a process that appears to be facilitated by up-regulation of adhesion molecules on the vascular endothelium in the brain and spinal cord (possibly induced by infection or an environmental toxin).[1,29,39] After migration into the CNS, pathogenic T cells are reactivated by myelin antigen fragments, which induce the secretion of cytokines that further disrupt the BBB and trigger an antibody cascade, leading to the acute inflammatory, demyelinating lesions of MS with axonal destruction.[1,34,39]

Most or many active MS lesions are clinically silent (ie, no clinical symptoms are present despite the presence of lesions on MRI). At least 1 Gd-enhancing lesion is present on a single MRI scan in about half of relapsing-remitting MS (RRMS) patients when the disease is clinically inactive. The appearance of new or enlarging Gd-enhancing lesions or newly recognized or enlarging T2 lesions not actively enhancing have been shown to exceed clinical relapses 10-20 fold when viewed on serial MRI scans.[9] Thus, tissue damage in most untreated RRMS patients is occurring in episodic but ongoing fashion despite periods of clinical quiescence.[9]

A SUMMARY OF LESION EVOLUTION

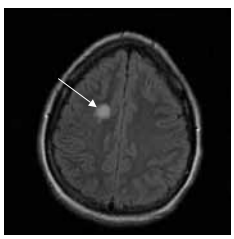
MRI is the most sensitive and noninvasive method to assess the sequence of pathological events underlying MS lesion

evolution.[34] A typical pattern of evolution can be seen on cMRI. In simplest terms, characteristic lesion patterns in early stages are enhancement postinjecton of Gd-containing contrast on T1-weighted imaging, hyperintensity on T2-weighted images, and either hypointensity or isointensity on noncontrast T1 images.[22,30,34] **Figures 2 and 3**[3] show typical T2-weighted, FLAIR, Gd-enhanced, and T1 noncontrast images in RRMS patients, highlighting an advantage of FLAIR.

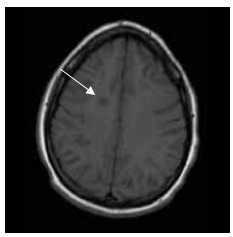
Virtually all new lesions in previously normal-appearing white matter (NAWM) are announced by nodular or ring-enhancing areas of Gd enhancement on T1 imaging reflecting BBB disruption; this almost always is associated with a corresponding hyperintense lesion on T2 images. About two-thirds of larger enhancements correspond to hypointense lesions on noncontrast T1-weighted images.[22] Most enhancing lesions fade over several weeks[3,22]; approximately half of hypointense lesions will resolve in about 1 month, and a return to isointensity may indicate remyelination.[22]

T2 lesions, representing brain tissue changes, gradually reduce in both size and intensity as edema resolves, but they usually persist for years. Hypointensity on T1 images may be present in persisting T2 lesions. Enhancing lesions that are potentially more aggressive show ring-like propagation of the enhancement for weeks or longer before they fade.[22] Some larger T1 hypointense lesions that contract over time, showing evidence of repair, often are accompanied by a loss of tissue surrounding the lesion.[22]

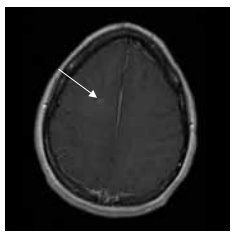
FIGURE 2: MS Lesions on Conventional MRI



T2 lesion on FLAIR



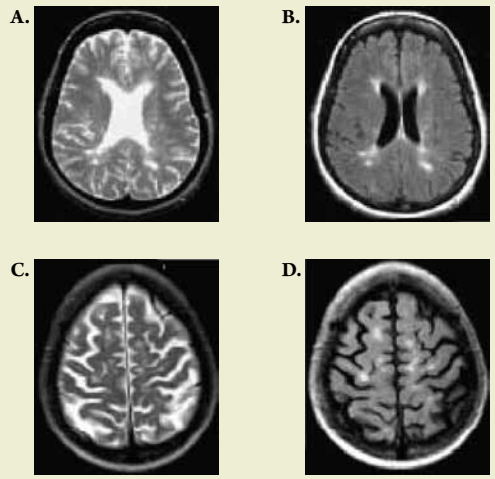
T1 hypointensity pre-contrast



T1 lesion post-contrast

Courtesy of Corey C. Ford, MD

FIGURE 3: Axial T2-Weighted and FLAIR Images in RRMS[3]



Axial T2-weighted (A) and FLAIR (B) images of a 35-year-old woman with relapsing-remitting MS. Axial T2-weighted (C) and FLAIR (D) images of a 33-year-old woman with relapsing-remitting MS. These images show the superiority of FLAIR in detecting both periventricular and juxtacortical supratentorial lesions.

The following discussion highlights in more detail what each of the 3 cMRI techniques indicate about MS pathology and its evolution.

T2-WEIGHTED IMAGES

T2-weighted images are highly sensitive to lesion detection in both WM and deep GM, revealing the spatial and temporal dissemination of MS lesions.[31] The appearance of new T2 lesions are a component of the diagnostic criteria for MS; the burden of T2 lesions in the patient with a CIS is a strong predictor of subsequent evolution to MS.[23] The sensitivity of T2 imaging has enabled earlier lesion detection as an aid to diagnosis and treatment with improved outcomes.[34]

FLAIR is one of the more effective sequences, particularly for deep GM lesions; the heavy T2 weighting with FLAIR maximizes contrast between lesions and normal tissue or CSF.[34] The confounding CSF signal is suppressed with this

technique by combining a CSF-nulling inversion recovery pulse with a long TR and TE that maximizes the lesion signal.[30] T2 lesions appear hyperintense and usually are ovoid in configuration, discrete, and sharply delineated; the major axes normally are perpendicular to the ventricular surface.[3,29,34] **Figure 4B-E**[22] further shows typical T2 lesion development in 4 patients with MS and the advantages of FLAIR. Gd-enhancing lesions (discussed below) are depicted in another patient in **Figure 4A**.

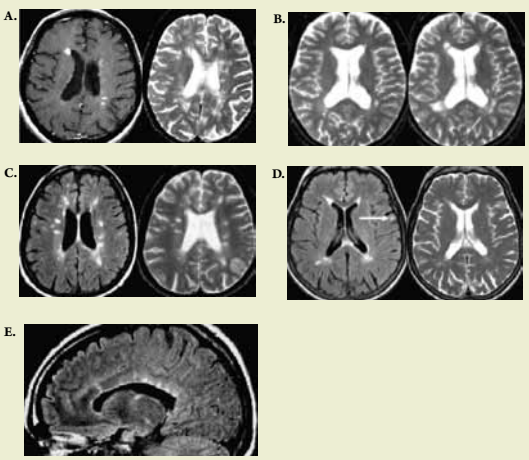
The basis for T2 hyperintensity on T2-weighted imaging is altered water content and mobility of protons (elevated T2 relaxation time of water molecules) in the various pathological components of T2 lesions.[22,30] However, hyperintensities are nonspecific with regard to the underlying causes of the altered water content/proton mobility (underlying pathology).[3,22,29,30] T2 hyperintensity seen on T2-weighted MRI may be related to edema or inflammation or to demyelination, axon loss, matrix destruction, and/or astrogliosis.[22,30] Microscopic analysis of chronic T2 lesions has revealed much heterogeneity; demyelination predominates in some lesions, whereas more severe injury with axonal loss and matrix disruption is present in others.[29,30] The lack of pathologic specificity of T2 lesions is considered a major factor in the poor correlation between T2 lesion burden and disability.[29] However, T2 metrics remain a valuable measure of disease activity over time in MS.[30]

T2 lesions generally shrink over time. After reaching their maximum size in 2-8 weeks, these lesions decrease in size over weeks to months. The reduced size and residual focal T2 hyperintensity is a footprint of a prior acute event.[29] Once stabilized in this smaller form, most chronic MS lesions show little change, even after years of observation.[30] However, some will expand peripherally or centrally due to renewed activity, and reactivation of focal lesions may be an important mechanism for more severe cumulative pathology, including impaired remyelination ability.[30]

The T2 lesion load (total lesion number and/or volume) quantitatively reflects burden of disease (BOD),[2,5] which varies among patients. In general, there is an increase in lesion number or volume in the brain and/or spinal cord over time. Lesions also may be prevalent early in MS, even prior to the initial clinical event.[9] In patients with a CIS in the **C**ontrolled **H**igh-Risk Subjects **A**vonex **M**ultiple Sclerosis **P**revention **S**tudy (CHAMPS), lesion volume in the placebo group was approximately 2 mL at baseline and increased by median increments of 0.04 mL and 0.31 mL at 6 months and 18 months, respectively; this corresponded to 2.8 and 5.0 new T2 lesions.[30,46]

An increase in lesion number or volume of approximately 10% per year typically is seen in patients with RRMS, with absolute volume increases of 0.4-0.75 mL/year.[30,34] Lesion load generally

FIGURE 4: Typical Features of MS on Conventional MRI[22]



Montage of 5 patients showing MRI features typical of MS.

A. Post-contrast (left) and CSE T2-weighted (right) images are shown of a 51-year-old woman with RRMS. Note several enhancing foci in the periventricular region bilaterally. Lesions have a homogeneous appearance and show corresponding hyperintensity on the T2-weighted image.
B. Baseline (left) and 5-year follow-up (right) CSE T2-weighted images of a 46-year-old woman with RRMS. EDSS score increased from 2.0 to 3.5 during this time. Note progressive number and total volume of T2 hyperintense lesions.
C. FLAIR (left) and FSE T2-weighted (right) images of a 41-year-old woman with RRMS and EDSS score of 3 illustrates the superiority of FLAIR for the detection of periventricular lesions. Note the characteristic appearance of the lesions, including an oval/ovoid morphology, size 5 mm or greater in diameter, and tendency to directly abut the ventricular margin.
D. FLAIR (left) and FSE T2-weighted (right) images of a 51-year-old woman with RRMS and EDSS score of 4 shows the superiority of FLAIR for the detection of cortical/juxtacortical lesions. Note the lesion in the left temporal lobe (arrow) seen by FLAIR but not on the T2-weighted image.
E. Sagittal FLAIR of a 27-year-old woman with RRMS shows typical perivenular orientation of lesions. Note the lesions are perpendicular to the long axis of the lateral ventricles, giving an appearance known as "Dawson's fingers."

EDSS= expanded disability status scale

is greater in secondary progressive MS (SPMS) with much variability; increases in volume of 0.1-2.0 mL/year have been reported.[30] Multiple focal lesions eventually may become confluent, such that there is additional T2 hyperintensity from secondary degeneration.[29] Atrophy between lesions may account for seamless confluence over time.[30]

Spinal Cord T2 Lesions

T2 hyperintense lesions are common in the spinal cord, occurring in 50%-90% of MS patients.[3,47] Approximately 20% of cases of MS involve only the spinal cord with no intracranial plaques on imaging.[2,48]

Studies have shown that spinal cord lesions tend to correlate with the number of brain lesions, and thus may be more prevalent as the disease progresses.[29] T2 spinal lesions are rare with normal aging in contrast with T2 hyperintense cerebral brain lesions that may occur naturally in the aging process. Therefore, the presence of spinal T2 hyperintensity can strengthen the confidence of a MS diagnosis.[2,29]

T2 hyperintense spinal cord MS lesions usually involve only 1 or 2 contiguous spinal levels and < 50% of cord cross-sectional area (**Figure 5**).[3] Lesions exceeding these boundaries suggest non-MS myelitis, including neuromyelitis optica (NMO).[3] Short-tau inversion recovery (STIR) or phase sensitive inversion recovery (PSIR) imaging appear to be the best methods for identifying spinal cord lesions, including chronic lesions not readily seen with other techniques.[4,49,50]

GM T2 Lesions

MRI studies consistently have shown GM involvement in MS occurring in both the cortex and basal ganglia.[41,51] It is present early in the disease process and correlates only partially with disease burden in WM.[41] However, GM lesions (compared with those in normal WM) often are missed by conventional T2-weighted images due to their longer relaxation times.[5,41] Use of fast-FLAIR sequences generally allow detection of more cortical and juxtacortical lesions than with conventional SE T2 imaging.[41] Higher-field scanners, such as 3.0 T or 8 T,[22,41] or advanced MRI techniques, such as dual inversion recovery,[51] offer improved GM lesion detection.

Studies assessing deep GM focal lesions are limited. However, some data suggest that basal ganglia T2 hyperintense lesions can be detected in about a quarter of MS patients.[41]

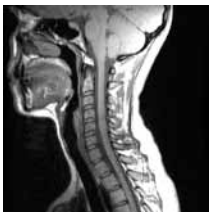
GD-ENHANCED T1 IMAGES

The lanthanide element Gd is paramagnetic in its trivalent state, lending its use as a contrast agent for MRI of the brain and spinal cord. By shortening the T1 of adjacent water protons, the signal intensity on T1-weighted scans is increased in areas of Gd uptake.[22,31]

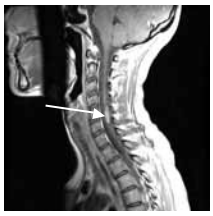
The occurrence of new lesions in previous NAWM appears as nodular areas of Gd enhancement on T1-weighted images.[5] These acute enhancing lesions are considered the first detectable event on cMRI and correlate with altered BBB permeability in the setting of perivascular inflammation. They almost always are associated with a high-signal intensity lesion at the same location on T2-weighted imaging (Figure 4A).[5,22,31]

On some occasions, enhancements may correspond to low-signal intensity on noncontrast T1-weighted imaging related to inflammation and edema.[4] Like T2 lesions, enhancing lesions at the time of a CIS are predictive of MS development.[30]

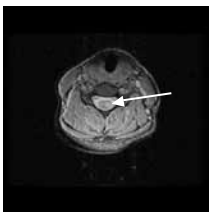
FIGURE 5: T1-Weighted, T2-Weighted, and Gd-Enhanced Spinal Cord Images



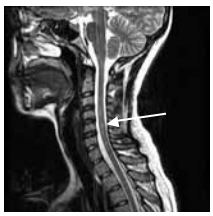
T1-weighted image pre-contrast showing no lesion.



T1-weighted image post-contrast showing an enhancing lesion.



T2 axial plane of the same lesion seen in the sagittal section.



T2-weighted image showing multiple lesions. The arrow is pointing to the enhancing lesion.

MS lesions in the spinal cord typically occupy no more than 1-2 levels and less than half of the cord cross-sectional area.

Courtesy of Corey C. Ford, MD

Visualization of enhancing MS lesions is secondary to leakage of contrast through disrupted junctions of vascular endothelium and accumulation in interstitial spaces of the CNS.[30] As an intact BBB is impermeable to MR contrast, appearance of the contrast on enhancement reflects induced disruption and permeability of the BBB due to MS-related inflammatory processes.[30]

Gd enhancement is transitory and is seen when acute inflammation is observed histologically. It then lessens and ceases as the inflammation subsides, usually 2-8 weeks postinjection of Gd-containing contrast[3,4,29,30]; however, time of enhancement varies considerably (1-16 weeks).[30] Evolution over time is shown in **Figure 6**.[29]

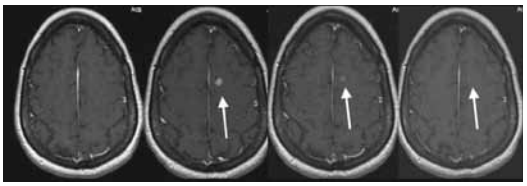
Enhancement usually accompanies the appearance of new lesions on T2-weighted imaging in patients with RRMS and SPMS and also may be the case in primary progressive MS (PPMS).[31] Some data have suggested that enhancing lesions are associated with subsequent brain atrophy, as well as an increased frequency of new enhancing lesions.[52]

Patterns of Gd enhancement vary. Most often, initial enhancing lesions are small, homogeneous nodules and may subsequently progress to ring-enhancing lesions (**Figure 7**).[2,22,29] Heterogeneous and tumor-like patterns also may occur.[3] Compared with homogenously enhancing lesions, ring-enhancing lesions tend to be larger, have a shorter duration of enhancement, and have a lower magnetization transfer ratio (discussed further). Ring enhancement is considered to represent more severe tissue damage and more aggressive forms of MS.[4]

Large enhancing lesions may have an incomplete or open ring, differing from the usual complete ring enhancement seen in patients with brain abscess or high-grade glioma.[34] An incomplete or open-ring enhancement, where the lesion abuts gray matter, is characteristic of MS.[22] A complete ring typically is seen when lesions are confined to white matter.[22]

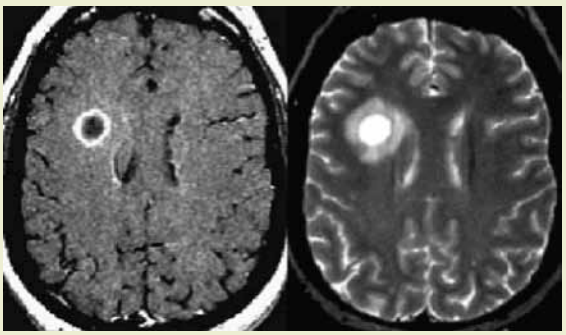
The usual contrast dose of Gd compounds is 0.1 mmol/kg. In research trials, triple doses (0.3 mmol/kg) of Gd and delayed imaging may be used, and the number of enhancing lesions detected has increased using this protocol in RRMS, SPMS, and PPMS.[30] However, this protocol is used rarely in clinical practice due to concerns for Gd toxicity, renal insufficiency, and cost. Furthermore, detecting additional lesions may not necessarily add value to clinical assessment or management planning in routine MS patient care. This dose also may increase lesion contrast and the percentage of patients with enhancing lesions.[30]

FIGURE 6: Time Course for Gd-Enhancing Lesions[29]



Serial monthly MRI shows new enhancing lesion after one month and expected decrease in size over subsequent 2 months, which corresponds to reduction in inflammation and return of the integrity of the blood-brain barrier breakdown.

FIGURE 7: Ring-Enhancing Lesion[22]



T1-weighted post-contrast (left) and CSE T2-weighted (right) images of a 48-year-old woman with RRMS show a ring-enhancing lesion and corresponding complex appearance on the T2 image.

Spinal Cord Enhancing Lesions

New spinal cord lesions also may be detected with Gd enhancement (Figure 5, page 13).[29] However, the presence or absence of enhancement is considered less reliable in the cord compared with the cerebrum related to spinal cord structure and technical reasons, such as pulsation artifacts and poor image quality.[29]

T1 HYPOINTENSE LESIONS

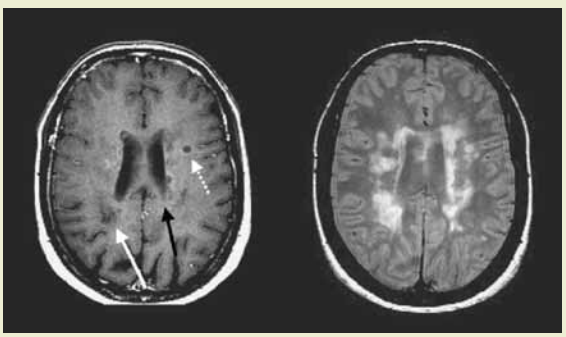
On noncontrast T1-weighted imaging, most MS lesions appear isointense in WM; however, some lesions are hypointense (lower signal intensity).[3,4,31] With corresponding T2-weighted images, this hypointensity is seen in approximately 5%-20% of T2-lesion areas compared with normal WM on T1-weighted imaging.[30]

Persistent T1 hypointense lesions represent an important MRI measure of significant tissue destruction. Acute T1 hypointense (edematous) lesions evolve over 3-9 months, with 40%-80% reverting to isointensity on T1 imaging—a process related to recovery from the edematous stage and possible remyelination.[4,22,29-31] However, 20%-60% (one-third on average) do not return to isointensity and remain hypointense. These chronic T1 hypointense lesions are classic T1 "black holes" and reflect severe demyelination, axonal loss, and matrix destruction.[29,30] **Figure 8**[29] depicts an edematous T1 hypointense lesion and a classic black hole. T1 black holes have been correlated with the subsequent development of brain atrophy in some studies.

It should be noted that some investigators consider T1 hypointensities to be black holes and chronic T1 hypointense lesion fraction to be "chronic black holes." This review supports chronic T1 hypointense lesions as true T1 black holes.

Black-hole lesion volume increases with the duration of MS and is greater in SPMS than in RRMS, which is indicative of a progressive disease course and less-efficient reparative processes in SPMS.[30,53] The net increase in T1 hypointense disease burden has been as high as 29% over 2 years in patients with RRMS.[5] In general, increases in T1 black holes parallel the increase in T2 lesion volume.[30]

FIGURE 8: T1 Hypointense Lesion Terminology[29]



(Left) In the left frontal white matter, a sharply-defined ring-enhancing lesion (dotted white arrow) is T1 hypointense on the basis of acute edema. The posterior right parietal white matter (solid white arrow) shows a classic, chronic, non-enhancing region of T1 hypointensity (ie, a T1 black hole), which is an area of more severe injury, as compared with other nonspecific T2 hyperintense regions without corresponding T1 hypointensity (black arrow, posterior left parietal-occipital white matter). (Right) T2-weighted image.

Baseline Gd-enhancing lesions on T1 imaging, especially ring-enhancing lesions, predict black-hole development—up to half of enhancing lesions persist as chronic T1 hypointense lesions.[4,31] Those acute T1 hypointense lesions showing a shorter duration and smaller amount of enhancement are more likely to become isointense over time.[3,31] Lesion size on enhancement appears to be linked to the lesion's evolution process. In one study involving RRMS and SPMS patients with > 5 Gd-enhancing lesions at baseline who were followed with monthly MRI for 6 months, smaller lesions (< 6 mm) were usually isointense at baseline and on T1-weighted imaging after 6 months, whereas larger lesions (> 6 mm) were often hypointense at baseline and on T1-weighted imaging at 6 months. Hypointensity also was more frequent for Gd-enhancing lesions of longer duration (ie, seen on 1-2 additional monthly scans) relative to Gd-enhancing lesions of short duration.[31]

It is important to distinguish acute T1 hypointense areas related to edema from chronic T1 hypointense lesions.[29,30] The former may show partial or complete recovery, whereas the latter are likely to be persistent. As serial imaging studies are not always available or practical, chronicity often can be assumed based on T1 hypointensity in the absence of contrast enhancement.[29,30] Corticosteroids may confound this interpretation by suppressing enhancement.[30] If possible, scans should be performed prior to or 1 month after administration of corticosteroids.

Black holes may be present even in the early stage of MS.[30] In the CHAMPS study, 1 or more black holes were evident in about half of patients showing 2 or more MRI-detected lesions following a CIS.[30] T1 black holes are only detected rarely in the spinal cord.[30]

T1 HYPERINTENSE LESIONS

Hyperintense areas on noncontrast T1 images are common in patients with MS, reportedly found in 78% of patients in one recent study.[54] The total number of lesions correlated

with both the degree of physical disability and brain atrophy as measured by MRI. The total number of T1 hyperintense lesions was found to be significantly higher in patients with SPMS compared with RRMS. Thus, early data suggest that the presence of T1 hyperintense lesions may be a useful biomarker of MS disease process, but more studies are needed to clarify their role in the monitoring of patients with MS.

LESION CORRELATIONS OVER TIME

In the early stages of MS, many focal T2 lesions may be counted, confluent lesions are rare, the T1 black hole number is low, and enhancing lesions can be seen in 30%-60% of patients.[29] With disease progression through relapsing and secondary progressive forms of MS, an increase in focal T1 and T2 lesion volume is seen, and there is an increasing confluence of lesions; brain atrophy also usually becomes apparent (enlarged third and lateral ventricles and thinning of the corpus callosum).[29]

Gd-enhancing lesion number and volume decline in SPMS, corresponding to the decrease in clinical relapses. A decreasing number of Gd-enhancing lesions may mark the transition from RRMS to SPMS,[23,29] although this remains controversial.[23] Some studies have suggested the most relevant marker of transition to the progressive phase of MS may be an increase in chronic T1 hypointense lesion burden at the expense of the T2 burden (increased T1/T2 ratio).[5] However, this also has been met with some controversy, and such data are not easily obtained, requiring serial segmentations followed over a prolonged time period.

Gd-enhancing lesions are relatively uncommon in PPMS related to less intense or less frequent inflammation.[23,29] However, research studies suggest that triple-dose gadolinium greatly increases the proportion of patients with PPMS who exhibit one or more enhancements on a random scan, particularly in those patients with a relatively short duration of disease.[55] This has important implications for clinical trials and clinical assessments of patients with PPMS.

4 CONVENTIONAL *MRI* IN THE DIAGNOSIS OF MS

Axonal loss occurs very early in MS.[56] Studies have shown that subclinical inflammatory events predate the occurrence of a CIS in about two-thirds of patients.[9] Studies also suggest that widespread tissue damage can be present in the earliest stages of disease.[9]

CLINICALLY ISOLATED SYNDROME

Studies demonstrate that approximately two-thirds of patients presenting with a CIS have multiple clinically silent brain lesions on baseline MRI typical of those seen in patients with MS, confirming that subclinical disease activity predates the initial clinical event.[57-60] CIS patients with baseline MRI lesions have a 50%-98% risk of being diagnosed with MS in the future compared with a < 25% risk in those with no detectable baseline lesions.[9,59,61-72]

RADIOLOGICALLY ISOLATED SYNDROME (RIS)

In 2006, an International Task Force defined 5 classes of clinically isolated syndromes based on clinical and MRI criteria. Type 5 CIS was defined as having no clinical symptoms or only nonspecific symptoms (eg, headache), but MRI shows abnormalities typical for demyelination. This subtype of a CIS also has been called a RIS. Patients with a type 5 CIS/RIS typically are identified incidentally when MRI is performed for other reasons than a concern for demyelinating disease (eg, headache or head trauma). In the absence of history and examination findings consistent with at least 1 clinical demyelinating event, a diagnosis of a CIS or MS is not possible. However, RIS patients should be followed closely as they may develop symptoms consistent with CNS demyelination and/or new MRI abnormalities characteristic of demyelination. In several studies of RIS patients, a CIS or MS has developed in about one-third of patients over 5 years.[73-75]

Early diagnosis and treatment offers the best chance to prevent irreversible tissue damage, delay or prevent progression to MS in patients with a CIS, and slow progression of disability in relapsing MS.[46,52,76-78] The National Clinical Advisory Board of the National MS Society (NMSS) strongly

advocates early treatment with a disease-modifying therapy (DMT) after a *definite diagnosis of MS with active disease or after a first attack and high-risk factors.*[79] It does not advocate early treatment when the diagnosis is uncertain or with a CIS in the absence of supportive risk factors.

Criteria for the diagnosis of MS are based on the demonstration of disease dissemination in time (DIT) and dissemination in space (DIS) in terms of CNS lesions.[47] In the past (1983 Poser criteria), diagnosis by these criteria was made almost entirely on clinical evidence and partially on CSF findings: 2 clinical events or episodes defined DIT and objective clinical evidence of more than 1 separate lesion defined DIS.[80,81] With these criteria, however, diagnosis of MS often was delayed. For the patient with a single attack plus a brain MRI suggestive of MS, waiting for a second attack was required before a diagnosis of MS could be made. This diagnostic process now can be expedited, as discussed further.

REVIEW OF DIAGNOSTIC CRITERIA

2001 McDonald Criteria

Formal integration of MRI into the diagnostic process took place in 2001 with publication of the McDonald criteria, also known as the International Panel (IP) criteria for the diagnosis of MS.[82] These criteria articulated the concept that documented new lesion formation on MRI was the diagnostic equivalent of a clinical relapse. The McDonald criteria were designed for use by practicing clinicians and in clinical trials. Included in the document were diagnosis of PPMS, clarification of the definitions used in MS diagnosis, and simplification of diagnostic classifications and descriptions.

However, the 2001 criteria guidelines did not emphasize the importance of MRI changes in patients with a CIS, and definitions for DIS and DIT were deemed too rigid by many neurologists. Furthermore, the relevance of spinal cord lesions was not addressed in the 2001 criteria.[77,83]

TABLE 4: 2005 McDonald Criteria for MS (Revisions to 2001 McDonald Criteria)[38]

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥ 2 attacks[a]; objective clinical evidence of ≥ 2 lesions	None[b]
≥ 2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: • MRI[c] *or* • ≥ 2 MRI-detected lesions consistent with MS plus positive CSF[d] *or* • Await further clinical attack[a] implicating a different site
1 attack[a]; objective clinical evidence of ≥ 2 lesions	Dissemination in time, demonstrated by: • MRI[e] *or* • Second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by: • MRI[c] *or* • ≥2 MRI-detected lesions consistent with MS plus positive CSF[d] *and* Dissemination in time, demonstrated by: • MRI[e] *or* • Second clinical attack[a]
Insidious neurological progression suggestive of MS	1 year of disease progression (retrospectively or prospectively determined) *and* 2 of the following: a. Positive brain MRI (9 T2 lesions or ≤ 4 T2 lesions with positive VEP)[f] b. Positive spinal cord MRI (2 focal T2 lesions) c. Positive CSF[d]

If criteria indicated are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS. If suspicious, but the criteria are not completely met, the diagnosis is "possible MS." If another diagnosis arises during the evaluation that better explains the entire clinical presentation, then the diagnosis is "not MS."

[a] An attack is defined as an episode of neurological disturbance for which causative lesions are likely to be inflammatory and demyelinating in nature. There should be subjective report (backed up by objective findings) or objective observation that the event lasts for at least 24 hours.

[b] No additional tests required. However, if tests are undertaken (MRI, CSF) and are negative, extreme caution needs to be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture and some objective evidence to support a diagnosis of MS.

[c] MRI demonstration of DIS must fulfill criteria listed in Table 6.

[d] Positive CSF determined by oligoclonal bands detected by established methods (isoelectric focusing) different from any such bands in serum, or by an increased IgG index.

[e] MRI determination of DIT must fulfill the criteria listed in Table 6.

[f] Abnormal VEP of the type seen in MS.

VEP=visual evoked potential

MRI changes in the CIS patient are of great importance. Studies before and after the development of the 2001 guidelines indicated a strong correlation between MRI-detected brain lesions in CIS patients as well as subsequent progression to clinically definite MS (CDMS).[67,77,84-88] In some of these studies, the presence of 1 or more lesions on baseline MRI was highly prognostic of MS occurrence (82%-88% of patients), albeit for some only after more than a decade of follow-up. In a study conducted by Brex et al,[87] 71 patients with isolated syndromes presumed to be demyelinating CNS events were followed for 14 years after baseline MRI. CDMS developed in 44 of 50 (88%) of those patients with 1 or more T2-weighted lesions at baseline compared with 4 of 21 (19%) patients with normal baseline scans.

2005 McDonald Criteria

The 2001 McDonald criteria were revised and updated in 2005 in an attempt to simplify earlier criteria, accommodate new published data, and address prior limitations.[38,47,89] The 2005 revised McDonald criteria (**Table 4,**[38] page 17) enable a more rapid and potentially more accurate diagnosis of MS, thereby providing the opportunity for earlier decisions regarding the initiation of DMT.[5,38,56] Lesions seen on MRI in different locations could be used to satisfy the DIS criteria, and those developing over time could be used to satisfy DIT. More specifically, the 2005 guideline changes expanded the role for spinal cord lesions to define DIS while retaining the 2001 DIS findings for brain abnormalities and allowance of new T2 lesions occurring any time after 30 days from onset of a CIS to represent evidence of DIT. The 2005 McDonald criteria also provided guidelines for establishing a diagnosis of probable MS in patients presenting with a CIS. Additionally, criteria for a diagnosis of PPMS were simplified in the 2005 McDonald criteria (**Table 5**[38]).

TABLE 5: Diagnosis of MS in Disease With Progression From Onset[38]

Original McDonald Criteria	2005 Revisions
1. Positive CSF *and* 2. Dissemination in space by MRI evidence of ≥ 9 T2 brain lesions *or* • ≥ 2 cord lesions or 4-8 brain lesions and 1 cord lesion *or* • Positive VEP with 4-8 MRI lesions *or* • Positive VEP with < 4 brain lesions plus 1 cord lesion *and* 3. Dissemination in time by MRI *or* • Continued progression for 1 year	1. 1 year of disease progression (retrospectively or prospectively determined) 2. *Plus* 2 of the following: a. Positive brain MRI (9 T2 lesions or ≥ 4 T2 lesions with positive VEP b. Positive spinal cord MRI (2 focal T2 lesions) c. Positive CSF[a] (isoelectric focusing evidence of oligoclonal IgG bands or increased IgG index, or both)

[a]MRI demonstration of space dissemination must fulfill the criteria derived from Barkhof and colleagues and Tintore and coworkers.
VEP=visual evoked potential

TABLE 6: 2005 McDonald MRI Criteria for DIT and DIS[47]

DIT:

There are 2 ways to show dissemination in time using imaging:
- Detection of gadolinium enhancement at least 3 months after the onset of the initial clinical event, if not at the site corresponding to the initial event
- Detection of a new T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event

DIS:

Three of the following:
- At least 1 Gd-enhancing lesion or 9 T2-hyperintense lesions if there is no Gd-enhancing lesion
- At least 1 infratentorial lesion
- At least 1 juxtacortical lesion
- At least 3 periventricular lesions

Note: A spinal cord lesion can be considered equivalent to a brain infratentorial lesion: an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions.

The criteria for DIS and DIT from the 2005 McDonald criteria are shown in **Table 6**.[38,47] Using the criteria for DIS, the patient with 1 spinal cord (infratentorial) lesion and 1 juxtacortical lesion would minimally qualify for DIS.[5] The DIT criteria were based on evidence that most Gd-enhancing lesions cease to enhance over a period of about 2 months and knowledge that new MS lesions can appear for only days or weeks after a single clinical event. In addition, the 30-day interval in the definition of DIT was based on a clinical attack requiring a stable interval of at least 30 days between clinical events.[5]

The need for clinical assessment in addition to MRI was emphasized in the 2005 McDonald guidelines, including exclusion of mimicking conditions and classification of symptoms and signs as monofocal (single lesion) or multifocal (more than one lesion), which are fundamental to the concepts of DIT and DIS.[38]

American Academy of Neurology (AAN) Criteria

In the interim between developing the 2001 McDonald criteria and 2005 McDonald revisions, the Therapeutic and Technology Subcommittee of the AAN concluded that available studies did not support the use of the 2001 McDonald criteria for DIS, which were considered less sensitive than the 1983 Poser criteria.[60] After extensive evaluation of the clinical literature, particularly in patients with a CIS, this subcommittee advanced specific recommendations for the use of MRI in diagnosing patients with suspected MS (**Table 7**[60]). However, these criteria were biased to data derived from clinical trials of a CIS that required the presence of 2 or more cerebral T2 lesions for study entry.

AAN guidelines are based upon the presence of occult disease activity (lesions) in the majority of patients presenting with first symptoms and the high correlation of these findings with subsequent development of MS. As a precautionary note, when the AAN guidelines were applied in a clinical/radiological center, false-positive rates were substantially higher than suggested by this taskforce.[47]

TABLE 7: Diagnostic Recommendations of the AAN[60]

MRI changes seen in MS are known to be nonspecific. Therefore, the information derived from imaging investigations always must be considered in the context of the specific clinical situation presented by an individual patient. As a result, the following recommendations are predicated on the exclusion, at baseline, of appropriate alternative conditions that can mimic MS or can mimic the radiographic findings seen in MS.

1. On the basis of consistent class I, II, and III evidence, in patients with a CIS, the finding of 3 or more white matter lesions on a T2-weighted MRI scan is a very sensitive predictor (> 80%) of the subsequent development of CDMS within the next 7 to 10 years (Type A recommendation). It is possible that the presence of even a smaller number of white matter lesions (eg, 1 to 3) may be equally predictive of future MS, although this relationship requires better clarification.
2. The presence of 2 or more Gd-enhancing lesions at baseline is highly predictive of the future development of CDMS (Type B recommendation).
3. The appearance of new T2 lesions or new Gd enhancement 3 or more months after a clinically isolated demyelinating episode (and after a baseline MRI assessment) is highly predictive of the subsequent development of CDMS in the near term (Type A recommendation).
4. The probability of making a diagnosis other than MS in patients with a CIS with any of the above MRI abnormalities is quite low, once alternative diagnoses that can mimic MS or can mimic the radiographic findings of MS have been excluded (Type A recommendation).
5. The MRI features helpful in the diagnosis of PPMS cannot be determined from the existing evidence (Type U recommendation).

TABLE 8: Diagnostic Criteria of Swanton et al[88]

DIS	DIT
One or more lesions in each of 2 or more characteristic locations: periventricular, juxtacortical, posterior fossa, spinal cord All lesions in symptomatic region excluded in brainstem and spinal-cord syndromes	A new T2 lesion on follow-up MRI, irrespective of timing of baseline scan

2006 Swanton MRI Criteria

Although the 2005 McDonald criteria attempted to simplify the 2001 McDonald guidelines, they are still somewhat complicated to use.[47] Applicability of the 2005 McDonald criteria by some neurologists and radiologists with less experience in diagnosing MS might be associated with specific implementation problems.[47]

In 2006, Swanton and colleagues proposed new imaging criteria (Swanton criteria) in an attempt to further simplify the diagnosis of MS in patients with a CIS.[88,90] They defined DIS as 1 or more T2-weighted lesions in at least 2 of 4 areas considered characteristic for demyelination, and they defined DIT as a new T2 lesion on follow-up MRI. There is no requirement for a Gd-enhancing lesion in the Swanton criteria (**Table 8**[88]).

Comparison of Swanton Criteria With 2001 and 2005 McDonald Criteria

A 2007 retrospective study by Swanton et al[88] compared these 3 sets of criteria in patients with a CIS (N = 282) who had undergone 2 MRI scans within 1 year of a CIS onset. In approximately 75% of patients, specificity and sensitivity of MRI criteria for MS were assessed for 3 years, and Cox proportional analysis was performed in all patients regardless of follow-up time. High specificity for detecting conversion to CDMS was shown for all 3 criteria: 91% for 2001 McDonald, 88% for 2005 McDonald, and 87% for Swanton. Sensitivity was lower for the 2001 McDonald (47%) than either the 2005 McDonald (60%) or the Swanton criteria (72%).

These data indicate that the 3 methods show similar specificity and can provide a reliable diagnosis of MS during the first episode following a CIS onset; the Swanton criteria are easier to apply clinically and may offer somewhat greater sensitivity compared with the 2005 McDonald criteria.

However, this was a retrospective analysis involving only 4 European centers. A large, prospective comparison is indicated to confirm these findings. In conclusion, the McDonald 2005 criteria currently are the most widely accepted diagnostic criteria in clinical practice, but this should change based on the recently published McDonald 2010 criteria.

MAGNIMS Criteria

In 2007, MAGNIMS, a European multicenter collaborative research network, met to review existing criteria for MS in CIS patients.[91] Their goal was to simplify MRI diagnostic prerequisites without reducing their specificity and to provide details of image interpretation and timing of MR imaging in the diagnosis of MS. These criteria specified DIS and DIT and proposed a new diagnostic algorithm based on MRI findings. In summary, MAGNIMS criteria specify:

1. To diagnose MS, an MRI scan performed at any time showing DIS and ≥ 1 asymptomatic Gd-enhancing lesion and noncontrast lesion (evidence for DIT) is sufficient.
2. If an MRI performed at any time shows DIS but no enhancing lesions or all lesions enhancing (no evidence of DIT), another MRI is required to demonstrate new T2 or Gd-enhancing lesions.
3. An abnormal MRI performed at any time that does not show DIS or DIT requires further MRIs to confirm DIS and DIT.[91]

The MAGNIMS algorithm and criteria has been incorporated into the new 2010 McDonald criteria.

2010 McDonald Criteria

The 2005 McDonald criteria were revised and updated in 2010 by the International Panel on Diagnosis of MS as new data and consensus necessitated simplification to enhance the criteria's comprehensiveness and utility, along with evaluating their applicability in additional patient populations. The IP recommended significant changes in the imaging criteria for DIS and DIT[8] based on the recently published data by MAGNIMS researchers.[88,91,92] The new criteria simplifies the requirements for the delineation of both DIS and DIT with fewer MR images, and it is anticipated that these changes may result in increased sensitivity without sacrificing specificity. Additionally, the IP expressed specific guidance on their use in pediatric, Asian, and Latin American patient populations (they were derived primarily from adult Caucasian European and North American populations).[8]

The McDonald criteria only should be applied in those patients who present with a typical CIS suggestive of MS or with symptoms consistent with a CNS demyelinating disease (the development and validation of the criteria have been limited to patients with such presentations). Additionally, it is imperative to consider and exclude alternative diagnoses when applying the McDonald criteria.[93,94]

MRI Criteria for DIS

In previous versions of the McDonald criteria, the Barkhof/Tintoré criteria were utilized in the determination of DIS, and applying them consistently was challenging. Therefore, the MAGNIMS researcher network compared the Barkhof/Tintoré criteria for DIS with the simplified Swanton-based criteria. In MAGNIMS, DIS can be detected with ≥ 1 T2 lesion in at least 2 of the 4 areas considered characteristic for MS (periventricular, juxtacortical, infratentorial, and spinal cord). In patients with spinal cord or brainstem syndromes, lesions in symptomatic regions are excluded and do not contribute to the lesion count. In the analysis of patients with a CIS, the Swanton-based criteria were simpler to apply and slightly more sensitive, without compromising specificity, than the original McDonald criteria for DIS. Consequently, the IP accepted the MAGNIMS DIS criteria, which can simplify the diagnostic process by enhancing sensitivity without sacrificing specificity (**Table 9**).[8]

TABLE 9: 2010 McDonald MRI Criteria for Demonstration of DIS and DIT[8]

DIS can by demonstrated by:
≥ 1 lesion[a] in at least 2 of 4 areas: • Periventricular • Juxtacortical • Infratentorial • Spinal cord[b]
DIT can by demonstrated by:
1. A new T2 and/or Gd-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI 2. Simultaneous presence of asymptomatic Gd-enhancing and noncontrast lesions at any time

[a]Gd enhancement of lesions is not required for DIS.
[b]If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the criteria and do not contribute to lesion count.

MRI Criteria for DIT

In the 2005 McDonald criteria, the MRI DIT evidence required an extra scan to confirm a diagnosis. In 2010, the IP accepted a new T2 lesion to establish DIT, regardless of the timing of the baseline MRI. It was determined that eliminating the requirement of an additional MRI after 30 days does not jeopardize specificity.[8]

MAGNIMS researchers confirmed results from previous studies demonstrating that a single brain MRI detecting DIS and asymptomatic Gd-enhancing and noncontrast lesions is highly specific for predicting early development of CDMS. It robustly can substitute for the prior imaging criteria for DIT. Thus, the IP allowed that the presence of both Gd-enhancing and noncontrast lesions on baseline MRI can substitute for an additional scan to confirm DIT if it can be determined robustly that the Gd-enhancing lesion is not due to non-MS pathology (Table 9). However, in patients whose imaging does not reveal both Gd-enhancing and noncontrast lesions on their baseline MRI, a new clinical event or serial MRI will be required to demonstrate a new enhancing or T2 lesion to establish DIT.[8]

By employing the revised simplified MAGNIMS criteria to fulfill DIS requirements and permitting DIT to be detected by a scan containing both enhancing and noncontrast lesions in various CNS regions typical for MS, a diagnosis of MS can be made in some CIS patients based on a single MRI. The IP felt this revision was warranted as it simplifies the diagnostic process while maintaining accuracy.[8]

Utility of CSF Findings in Diagnosis

The IP corroborated that positive CSF parameters (elevated immunoglobulin G [IgG] index or 2 or more oligoclonal bands [OCBs]) can be useful to support the inflammatory demyelinating process of the underlying pathology, evaluate alternative diagnoses, and predict CDMS. In the 2 previous versions of the McDonald criteria, a positive CSF finding could reduce the DIS requirements (2 or more MRI-delineated lesions consistent with MS). However, the IP does not believe that further attenuation of the MRI requirements in patients with positive CSF parameters is appropriate as the MAGNIMS criteria did not appraise the contribution of CSF values to the criteria for DIS and DIT. Additional studies are required to confirm the additional diagnostic value of CSF parameters.[8]

Diagnosis of PPMS

The diagnosis of PPMS based on the McDonald criteria was revised in 2005 and required (in addition to 1 year of disease progression) 2 of the 3 findings: positive brain MRI (9 T2 lesions or ≥ 4 T2 lesions with positive visual evoked potential (VEP); positive spinal cord MRI (2 focal T2 lesions); or positive CSF. In an effort to harmonize the MRI diagnostic criteria for all forms of MS and acknowledge the special diagnostic needs for PPMS, the IP recommends that the requirement of 2 out of 3 MRI or CSF findings be maintained with the substitution of the previous brain imaging criterion with the new MAGNIMS brain imaging criterion for DIS (**Table 10**).[8]

Application of McDonald Criteria to Pediatric, Asian, and Latin American Populations

The previous versions of the McDonald criteria were developed primarily from data utilizing adult Caucasian European and North American populations.[8] Therefore, the validity of extrapolating these criteria to other populations, especially pediatric,[95,96] Asians,[97] and Latin Americans[98] has been challenged.[8]

Pediatric MS

Greater than 95% of pediatric MS cases present as the relapsing-remitting course; PPMS is uncommon, and any consideration of such a diagnosis should prompt a detailed exploration of alternative diagnoses. Approximately 80% of pediatric and nearly all adolescent-onset cases present with attacks typical for an adult CIS, with a similar or greater burden of total T2 lesions. In pediatric patients younger

TABLE 10: 2010 McDonald Criteria for Diagnosis of MS in Disease With Progression From Onset[8]

PPMS may be diagnosed in subjects with:

1. One year of disease progression (retrospectively or prospectively determined)
2. Plus 2 of the 3 following criteria[a]:
   - A. Evidence for DIS in the brain based on ≥ 1 T2[b] lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial)
   - B. Evidence for DIS in the spinal cord based on ≥ 2 T2[b] lesions in the cord
   - C. Positive CSF (isoelectric focusing evidence of OCBs and/or elevated IgG index)

[a]If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the criteria.
[b]Gd enhancement of lesions is not required.

than 11 years of age, lesions are more ill-defined but larger than those in adolescence. A high level of sensitivity and specificity of imaging criteria for DIS has been demonstrated in pediatric MS.[8]

The Panel determined that the proposed MAGNIMS-based MRI revisions for DIS would fulfill the criteria well for most pediatric cases, especially those with acute demyelination presenting as a CIS. Most pediatric patients have > 2 lesions and are likely to have the lesions in 2 of the 4 specified CNS areas. At this time, the frequency of spinal cord lesions is unreported in pediatric cases, but the presence of spinal cord lesions in pediatric cases with spinal cord symptoms appears generally similar to that of adults.[8]

Approximately 15%-20% of pediatric cases (primarily those younger than 11 years old) present with encephalopathy and multifocal neurological deficits, which are difficult to differentiate from acute disseminated encephalomyelitis (ADEM). Currently, the international consensus criteria for MS diagnosis in pediatric patients with an ADEM-like first presentation require confirmation by 2 or more non-ADEM-like attacks or 1 non-ADEM attack followed by an accumulation of clinically silent lesions. Although pediatric patients with an ADEM-like first MS attack are more likely to have 1 or more noncontrast T1 hypointense lesions, 2 or more periventricular lesions, and the absence of a diffuse lesion pattern than children with monophasic ADEM, these characteristics are not particularly discriminatory. Additionally, the MRI scans of children with monophasic ADEM generally reveal variably enhancing lesions (often greater than 2) primarily located in the juxtacortical WM, infratentorial space, and the spinal cord. Therefore, it would be inappropriate to apply the revised MAGNIMS-based criteria for DIS and DIT on initial MRI; the use of serial clinical observations and MRI scans are recommended to confirm a diagnosis of MS. Following an initial attack in this young age group, significant lesion resolution can occur prior to the development of new lesions over time and attacks leading to a MS diagnosis.[8]

Asian and Latin American Populations

The IP focused on the difficult differential diagnosis of typical MS vs MS of NMO and NMO-spectrum disorders, which have a different pathophysiology, clinical course, prognosis, and response to therapies than typical MS. Among Asians with a CNS inflammatory demyelinating disease, a phenotype exists that is characterized by NMO, longitudinally extensive spinal cord lesions, and positive aquaporin 4 (AQP4) autoantibody seropositivity. This is relatively more common in Asians than in Western populations. The IP solicited advice on the application of the McDonald criteria in Asia and Latin America, where there is evidence of a similar phenotype distinction. Although the McDonald criteria are employed widely in other parts of the world, there is some uncertainty, especially in Asia, whether MS and NMO are unique and how to distinguish them.[8]

The IP recommended testing for AQP4 autoantibody via validated assays in those cases where NMO or NMO-spectrum disorders are suspected, especially in patients with an Asian or Latin American genetic background. The majority of patients with an NMO-like presentation will be AQP4-antibody positive, and those with MS are more likely to test negative. Current evidence suggests that once NMO and NMO-spectrum disorders are ruled out, Western-type MS in Asian or Latin American populations is not fundamentally different from typical MS in the Caucasian population; therefore, the MAGNIMS MRI criteria would apply. However, confirmatory studies should be performed.[8] Additional information may be obtained from Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria.[8]

Application of the McDonald Criteria: 2010 Revisions

For the diagnosis of MS, the IP recommends revisions to the McDonald criteria as delineated in **Table 11**,[8] focusing on the requirements for demonstrating DIS, DIT, and diagnosing PPMS. These 2010 revisions are likely to be applicable to pediatric, Asian, and Latin American populations once alternative diagnoses have been evaluated. However, the predictive validity of DIS and DIT from a single scan in pediatric patients with a CIS requires confirmation from additional studies. Additionally, the McDonald criteria have not been validated in Asian or Latin American populations; additional studies are required to confirm the sensitivity and specificity of the criteria in those populations.[8]

RECOMMENDATIONS FOR MRI IN MS DIAGNOSIS

The diagnosis of MS is a clinically based decision[41] and can be made on clinical grounds only.[38] MRI findings alone are insufficient to make a diagnosis of MS, and normal findings

TABLE 11: The 2010 McDonald Criteria for Diagnosis of MS[8]

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥ 2 attacks[a]; objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥ 2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: • ≥ 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; *or* • Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥ 2 lesions	Dissemination in time, demonstrated by: • Simultaneous presence of asymptomatic Gd-enhancing and noncontrast lesions at any time; *or* • A new T2 and/or Gd-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; *or* • Await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (CIS)	Dissemination in space and time, demonstrated by: For DIS: • ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; *or* • Await a second clinical attack[a] implicating a different CNS site; and For DIT: • Simultaneous presence of asymptomatic Gd-enhancing and noncontrast lesions at any time; *or* • A new T2 and/or Gd-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; *or* • Await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]: 1. Evidence for DIS in the brain based on ≥ 1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥ 2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of OCBs and/or elevated IgG index)

If the criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS; if suspicious, but the criteria are not completely met, the diagnosis is possible MS; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is not MS.

[a]An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, VEP response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b]Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

[c]No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

[d]Gd-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

on MRI do not exclude MS.[38,88] In simple terms, 2 clinical relapses over time with no other identifiable causes may constitute a diagnosis of MS even in the absence of other evidence, such as MRI or CSF findings. However, the value of MRI has been demonstrated over past decades, and virtually all neurologists also use MRI techniques and CSF findings to help diagnose MS.

The revised 2010 McDonald criteria do not rely solely on MRI to make a diagnosis; they are not applicable without a clinical evaluation of the patient.[38] Rather, they incorporate MRI into the diagnostic algorithm with other paraclinical methods, such as CSF analysis and evoked response studies, to demonstrate multiple areas of lesion involvement and use the appearance of uniquely appearing enhancing or noncontrast lesions to demonstrate lesion development over time.

When MRI is readily available, the following is recommended for patients with suspected MS:

1. Detailed history and physical examination: Assess degree of neurologic involvement and whether symptoms are typical of MS.[38,99]
2. MRI: Owing to their relative simplicity and practicality for the routine clinical setting, AAN criteria might be considered for patients presenting with a highly characteristic CIS (Table 7, page 19). However, for most patients, including those with evidence of progressive disease, the 2010 McDonald criteria are recommended. The use of more relaxed criteria (such as the AAN criteria) introduces the risk of false-positive diagnoses, particularly in patients with nonspecific findings.[29] The Swanton criteria were evaluated for inclusion into the 2010 McDonald criteria by the International Panel on Diagnosis of MS and have been incorporated accordingly as delineated above.
3. Differential diagnosis: Exclusion of other potential conditions that can mimic MS or mimic MRI findings observed in MS is paramount.[38,94] Some of these are listed in **Table 12**.[38,60,94,99,100] Spinal cord MRI is useful especially in excluding alternative diagnoses.[5,38] An alternative approach to differential diagnosis was provided by the MAGNIMS workshop, which defined MRI red flags that should alert clinicians to consider a possible diagnosis other than MS.[94] These red flags are designed to have more practical usefulness in everyday clinical practice, as opposed to a disease-oriented approach, and are shown in **Table 13**.[94]

   In 2008, Miller et al published proposed guidelines developed by the International Task Force for the differential diagnosis of MS in patients with CIS.[93] These guidelines provide a clear definition of a CIS; categorize clinical and paraclinical features of a CIS that are most typical of patients eventually diagnosed with MS; indicate red flags (features compatible with MS but could occur in other diseases); provide specific consensus-based algorithms for the differential diagnosis of the 3 most common CIS presentations related to MS (optic neuritis, spinal cord, and brainstem-cerebellar syndromes); and offer a classification system and diagnostic criteria for idiopathic disorders of the CNS.[93,101] Furthermore, this review provides detailed guidelines to differentiate MS in CIS patients from other idiopathic inflammatory demyelinating disorders, such as NMO and ADEM. This detailed guideline serves as an important clinical tool in the differential diagnosis of a CIS and MS.
4. Other tests: CSF analysis and/or VEP should be obtained in the context of the 2010 McDonald criteria or to further support a diagnosis. In the absence of an MRI facility, MS can be diagnosed based on clinical findings alone, but some form of neuroimaging likely will be indicated in most settings, even when MRI is not available.[38,47]

TABLE 12: Conditions That Mimic MS (Differential Diagnosis)[38,60,94,99,100]

- Acute disseminated encephalomyelitis
- Antiphospholipid antibody syndrome
- Behçet's disease
- CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
- Cavernous hemangiomata
- Cervical spondylosis
- Demyelinating polyradiculopathy (chronic inflammatory)
- Hereditary ataxias
- Hereditary paraplegia
- HIV infection
- Ischemic optic neuropathy (arteritic and nonarteritic)
- Leber's optic atrophy
- Leukodystrophies
- Lyme disease (neurologic)
- Lymphoma (CNS)
- Meningioma
- Migraine
- Neurosarcoidosis
- Spinal dural arteriovenous fistula
- Stroke
- Syphilis
- Systemic lupus erythematosus
- Sjögren's syndrome
- Vasculitis (CNS)
- Vitamin B_{12} deficiency

Spinal Cord Imaging

Spinal cord imaging is not indicated routinely in the patient with suspected MS. However, it can be used to confirm or refute a diagnosis of MS. Studies have shown that focal spinal cord lesions are rare in patients with neurologic conditions known to produce brain lesions mimicking MS but are present in most patients (up to 90%) with well-established MS.[5,47] MRI detection of spinal cord MS lesions, typically T2 hyperintense and at least 3 mm in size, is immensely helpful if DIS is not detected on brain imaging in patients with suspected MS.[38,47]

TABLE 13: MRI Red Flags Suggestive of a Diagnosis Alternative to MS[94]

	Disease
Brain white matter	
Normal	NMO (absent or few lesions), ATM
Large lesions	AMS (sometimes confluent and perilesional oedema), BCS (concentric whorls of alternating rings of enhancement), PACNS (with mass effect)
Symmetrically distributed lesions	ADEM, AFL
Poorly defined lesion margins	ADEM
Absent of rare Dawson fingers, corpus callosum, and periventricular lesions	ADEM
Absent MRI activity at follow-up	ADEM
T2 hyperintensity of the temporal pole, U-fibers at the vertex, external capsule, and insular regions	CADASIL
Multiple bilateral microhemorrhagic foci	CADASIL, SVD
Frequent sparing of corpus callosum and cerebellum	CADASIL, SVD
Lesions in the center of corpus callosum, sparing the periphery	Susac's syndrome
Hemorrhages	PACNS
Simultaneous enhancement of all lesions	ADEM, PACNS, sarcoidosis
Infarcts	SID, PACNS, SVD
Punctiform parenchymal enhancement	PACNS, sarcoidosis, NBD
Predominance of lesions at the cortical/subcortical junction	SID
Diffuse white matter involvement	NBD, encephalitis (HIVE), SVD, CADASIL
Cerebral venous sinus thrombosis	NBD
Large and infiltrating brainstem lesions	NBD
Anterior temporal and inferior frontal lobe involvement, associated with enhancement or mass effect	Encephalitis (HSE)
Isolated lesions with ring enhancement (often complete)	Abscesses
Mass effect	Abscesses
Multifocal, asymmetrical lesions starting in a juxtacortical location and progressively enlarging	PML
Large lesions with absent or rare mass effect	PML
Extensive and bilateral periventricular abnormalities in isolation	B_{12}D, ACD
Cortical gray matter	
Cortical/subcortical lesions crossing vascular territories	MELAS
Prevalent involvement vs white matter	Encephalitis
Infiltrating lesions that do not remain in gray or white matter boundaries	Abscesses
Deep gray matter	
Bilateral lesions	ADEM (at the gray-white-matter junction), CADASIL
Lacunar infarcts	CADASIL, SVD
T1 hyperintensity of the pulvinar	FD
Multiple discrete lesions in the basal ganglia and thalamus	Susac's syndrome
Large and infiltrating basal ganglia lesions	NBD
Infiltrating lesions without respecting gray or white matter boundaries	Abscesses
T2 hyperintense lesions in the dentate nuclei	AFL (CTX)
Spinal cord	
Large and swelling lesions	NMO (with corresponding T1 hypointensity), ADEM, ATM, Sjogren's syndrome
Diffuse abnormalities in the posterior columns	B_{12}D, ACD
Other	
No "occult" changes in the NAWM	NMO, Lyme disease, SID (except in NSLE)
Pontine lacunar infarcts	CADASIL, SVD
Dilation of Virchow-Robin spaces	HHC, PACNS
Diffuse lactate increase on brain MRS	MELAS
Meningeal enhancement	Susac's syndrome, PACNS, NBD, meningitis, Lyme disease, sarcoidosis
Hydrocephalus	Sarcoidosis
Absence of optic-nerve lesions	PML

ACD=acquired copper deficiency; AFL=adult forms of leukoencephalopathies; AMS=acute multiple sclerosis (Marburg type); ATM=acute transverse myelitis; B_{12}D=vitamin B_{12} deficiency; BCS=Balo's concentric sclerosis; CTX=cerebrotendinous xanthomatosis; FD=Fabry's disease; HHC=Hyper homocystinemia; HIVE=HIV encephalitis; HSE=herpes simplex encephalitis; MELAS=mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; NBD=Behcet's disease with CNS involvement; NSLE=neuropsychiatric systemic lupus erythematosus; PACNS=primary angiitis of the CNS; PML=progressive multifocal leukoencephalopathy; SID=systemic immune-mediated disease; SSP=subacute sclerosing panencephalitis; SVD=small-vessel disease.

In the McDonald criteria, a focal spinal cord lesion on MRI is considered equivalent to (and can be substituted for) a brain infratentorial lesion, and a Gd-enhancing spinal cord lesion is equivalent to an enhancing brain lesion. In addition, individual spinal cord lesions can be combined with the number of brain lesions to reach the required number of T2 lesions.

5 CONVENTIONAL *MRI* IN MONITORING DISEASE EVOLUTION OVER TIME: *Correlations With Clinical Status*

MRI is an important tool for monitoring the clinical status of MS patients over time. Some findings on MRI may correlate with disease activity and predict clinical status, which can assist with treatment decisions.[31,102,103] MRI-derived endpoints are used as primary and secondary outcome measures in MS clinical trials.[21]

There are 4 components readily visible on MRI that can be used by the clinician to assess disease activity over time in individual patients,[5] including:

- number and volume of lesions on T2-weighted imaging (T2 lesion load or T2 BOD);
- presence, number, and appearance of Gd-enhancing lesions;
- number and volume of T1-weighted hypointense lesions (T1 BOD); and
- net tissue loss or brain atrophy.

Correlations of the first 3 components listed with clinical status are discussed further. Brain atrophy as an indicator of disease progression is discussed under "Advanced MRI Techniques."

T2 BOD OVER TIME

Although attenuated by DMT, the number of MRI-defined T2 hyperintense lesions increases over time in all MS phenotypes, including those PPMS patients with an initially low T2 lesion burden.[5] Although T2 lesion volume is an overall measure of disease burden in MS, most studies have found only weak correlations between this and disability indices, such as the Kurtzke expanded disability status scale (EDSS) score; lack of correlation is particularly poor in individual patients.[22,23,29-31,34] For example, in one small study involving RRMS patients followed for 2 years (N = 18), an insignificant correlation was observed between T2 BOD, EDSS scores, and disease duration despite a substantial increase in T2 BOD during this period.[31] There may be a higher correlation between changing T2 burden and degree of cognitive impairment than physical disability.[23]

Some longitudinal studies suggest T2 BOD has prognostic value for long-term disability (EDSS) when assessed in early MS (eg, the first 5 years in patients with a CIS). This correlation decreases or is lost in patients with longer-standing disease.[23,30,31,87,103]

The overall lack of significant T2 lesion correlation with disability stems largely from the lack of pathological specificity of the T2 lesion.[30] T2 lesion load also does not reflect the contribution of underlying pathology in NAWM to disability.[30]

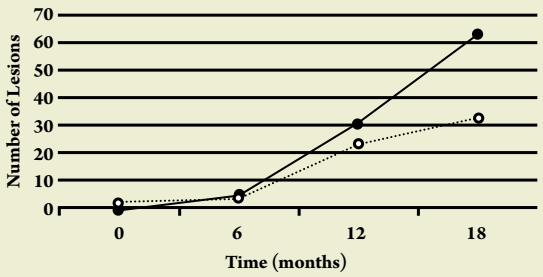
The "clinical MRI paradox" is clearly evident for T2 BOD, because what is seen on MRI may not always manifest clinically, particularly in individual patients.[21,31] This paradox also is evident for Gd-enhancing lesions (discussed below) and has led to investigation of other MRI measures, such as T1 black holes and whole-brain atrophy. Nevertheless, the T2 BOD is a useful index of disease burden in MS and should be considered a global measure of potential disability. It certainly appears to be a reasonable indicator of previously affected cerebral tissue.

GD-ENHANCING LESIONS

The sensitivity of Gd-enhanced MRI is 5-10 times greater than clinical findings for the assessment of disease activity.[104] This was shown by Barkhof and colleagues in 1992, where 5-10 MRI events (new lesions) were seen for every clinically apparent event.[104] Much higher lesion/event ratios, up to 100:1, have been reported in some patients.[29,30] Thus, the correlation between enhancing lesions and relapses would seem to be poor, and this negative relationship has been shown in several cross-sectional studies.[4,29-31] Lack of correlation with both T2 burden and enhancing lesions in a patient from the CHAMPS trial is illustrated in **Figure 9**.[30]

There is some evidence that the presence of continuing Gd-enhancing lesions may indicate a higher risk of relapse over the short or intermediate term and may contribute to long-term clinical dysfunction.[4,31] However, data from the Sylvia Lawry Center for MS Research was not supportive of the

FIGURE 9: Enhancing Lesions and Relapses[30]



MRI results from one untreated patient from the CHAMPS trial (Controlled High-Risk Subjects Avonex® Multiple Sclerosis Prevention Study). Enhancing lesions (open circles) and/or new or enlarging T2-hyperintense lesions (filled circles) reveal marked activity, yet during the 18-month evaluation there were no new clinical events. The patient developed 63 new or enlarging T2 lesions and had 33 enhancing lesions during the 18 months of follow-up.

role of enhancing lesions as a reliable surrogate for relapses in MS. This study rigorously examined whether enhancing lesion activity over time on serial imaging could have a strong concomitant (cumulative numbers of enhancements on monthly imaging over 6 months and relapses over the same interval) and predictive (cumulative numbers of enhancements on monthly imaging over 6 months and relapses over the subsequent 6-month interval) relationship with clinical attacks and might serve as a surrogate measure for clinical outcomes in therapeutic trials.[6] While concomitant and predictive relationships were correlated, they were not robust enough to suggest that enhancements could be a true surrogate for relapses.

More recent studies, notably by Sormani and Bonzano, have examined the effects of treatment on clinical relapses, EDSS scores, and MRI activity. In these studies, a strong correlation was found between treatment effect on clinical relapses and MRI activity that supported the use of commonly used surrogate markers of EDSS worsening in clinical trials. Other studies have found that MRI markers for clinical relapses have been found to be reliable, but their relationship to disability progression is still controversial. Further trials are indicated to define the effects of treatment on surrogate disease markers at the individual patient level.[105-107]

Although lesion enhancement is observed during acute relapses, the lesion/event ratios described above indicate that most relapses are clinically silent. This supports the presence of subclinical disease activity persisting between clinical relapses in MS when the patient and physician consider the disease clinically stable.[29,34] Ring-enhancing lesions suggest greater tissue damage and more aggressive MS,[4] and they have been shown to be strong predictors of persistent T1 hypointense lesions (black holes) and subsequent development of brain atrophy.[31]

In general, with occurrence of enhancing lesions in functionally sensitive regions of the CNS, the imaging findings, symptoms, and electrophysiological disturbances share a similar time course.[30] Thus, at times, acute enhancing lesions may correspond temporally and spatially with symptoms and other paraclinical measures. Although the correlation between clinical MS and existence of enhancing lesions is weak, enhancing lesions represent ongoing inflammation and are a useful biomarker for monitoring responses to drug therapies known to have an anti-inflammatory component of action.[30]

Gd enhancement is only a moderately accurate predictor of the development of cumulative disability of MS over time.[3,22,23,29,31,108] In a meta-analysis of studies regarding the natural progression of RRMS and SPMS (natural-history studies and placebo groups in clinical trials), Kappos et al[108] found that changes in EDSS scores at 1 or 2 years were only weakly predicted by the number of Gd-enhancing lesions at baseline. Similar weak results of predictive value also were found using the first 6 monthly scans. The change in the number of Gd-enhancing lesions, however, was somewhat predictive of relapse during the first and second years. These data suggest that inflammatory activity on MRI, as evidenced by enhancement, occurs during relapses, but additional pathogenic mechanisms contribute to the overall development of functional deterioration and long-term disability.[31]

T1 BOD

T1 BOD correlates with disability in MS, but the association is not always strong.[22,30] This may be related in part to terminology differences (ie, general T1 hypointensity vs chronic T1 hypointense lesions) and the degree of damage within the T1 black hole. In general, darker T1 black holes indicate greater axonal damage and loss.[4] Therefore, considering these factors, individual patients with a similar number of study-defined "black holes" may exhibit different levels of clinical disability.[4]

Although only a modest association of T1 hypointense lesions and disability has been reported in some studies,[22] cross-sectional studies have shown that T1 BOD correlates better with clinical disability (EDSS) than the T2 hyperintense lesion burden.[3,30,31,53] This may be most evident in patients with SPMS.[3] Patients with the apolipoprotein E-epsilon 4 allele have a greater tendency to increase their proportionate T1 BOD.[3] Some investigators have postulated that T1 black holes are a relevant marker of progressive tissue damage and clinical evolution in patients with established MS.[31]

Chronic T1 hypointensities (T1 black holes) represent severe tissue injury of varying degrees, much of which is subclinical.[30] As mentioned earlier, T1 BOD has correlated with the development of brain atrophy in some studies, and brain atrophy has been shown to correlate relatively strongly with disability in MS.[4,32] In one study involving RRMS and SPMS patients (N = 29), progressive cerebral atrophy was significantly correlated with the increase in T1 lesion volume over 18 months, but there was no significant correlation of atrophy and T2 BOD.[109]

6 CONVENTIONAL *MRI* IN ASSESSING RESPONSE TO MS THERAPIES

Since 1993, several DMTs have been approved by the United States Food and Drug Administration (FDA) for the treatment of MS. The first-line agents approved for the treatment of relapsing MS include interferon (IFN) beta-1a given intramuscularly (IM); IFN beta-1a given subcutaneously (SC); IFN beta-1b given SC; glatiramer acetate given SC; and the newly approved oral agent, fingolimod. Currently, second-line agents include mitoxantrone given intravenously (IV) and natalizumab given IV. The availability of these agents likely would not have been possible without the use of MRI as a secondary—but highly supportive—outcome measure in clinical trials.[110] In clinical trials involving patients with RRMS or SPMS, T2 BOD often is used as a secondary endpoint in phase III trials, and enhancing lesions frequently serve as the primary outcome measure in phase II studies.[29] T1 black holes also have been included as a secondary outcome measure in some trials.[37]

MRI MEASURES OF TREATMENT RESPONSE

All FDA-approved DMTs have demonstrated significant clinical efficacy as well as a reduction in MRI measures of disease activity in MS clinical trials.[62-66,68,84,111-114] Despite a similar treatment response rate for the first-line agents as measured by relapse frequency,[52,115-118] reductions in lesions as seen on MRI have varied more widely by treatment; however, statistically significant reductions in either T2 lesions, Gd-enhancing lesions, or both usually were observed. For example, in the pivotal SC IFN beta-1b trial, T2 lesion burden was reduced significantly by SC IFN beta-1b relative to placebo (-0.1% vs 20%), but enhancing lesions were not measured.[68] Enhancing lesions (but not T2 lesion volume) were decreased significantly in the pivotal trial with IM IFN beta-1a.[65]

The initial large trial with SC IFN beta-1a detected a significant reduction in both T2 lesion burden and Gd-enhancing lesions. T2 burden of disease was reduced by 3.8% over 2 years in patients receiving the higher dose of SC IFN beta-1a compared with an increase of 10.9% in the placebo group.[66] Similar activity was seen in the seminal MRI study with glatiramer acetate where new T2 lesions and total new enhancing lesions were reduced significantly.[3] T2 lesion volume was reduced 40% by glatiramer acetate compared with placebo during the 2-year trial. Extensions of early pivotal clinical trials with first-line agents showed sustained benefits on MRI disease measures.[119-121]

T1 black hole formation has been reduced by glatiramer acetate and IFN beta in patients with RRMS and SPMS.[22,122] In a study by Morgen and colleagues, a correlation was shown to exist between the occurrence of Gd-enhancing lesions and black holes in RRMS patients receiving SC IFN beta-1b.[123] In patients with at least 1 enhancing lesion after 1 year of therapy, an increase in T1 black hole volume was seen during the subsequent 2 years of therapy.

With IFN beta preparations, a decrease in Gd-enhancing lesion number and volume usually is seen after 3-4 weeks, and this effect is sustained over treatment intervals of years in the majority of patients. The duration of effect or washout after discontinuing therapy appears to be 6-10 months

based on limited data.[29,30] The time course of enhancing lesion suppression by glatiramer acetate therapy has been demonstrated in serial MRI studies with the effect increasing to statistically significant levels within 4-6 months.[30] Natalizumab also rapidly suppresses enhancing lesions.[30]

Evidence from 2 key trials, FREEDOMS and TRANSFORMS, supports the efficacy of fingolimod in terms of MRI outcomes in relapsing MS. In the FREEDOMS trial, patients with RRMS were randomized to receive fingolimod 0.5 mg, 1.25 mg, or placebo. Results showed a significant reduction in the annualized relapse rate in both fingolimod groups compared with placebo, and there was a reduction in MRI disease activity.[124] In both fingolimod treatment groups, MRI-related measures (including number of new or enlarged lesions on T2-weighted images, Gd-enhancing lesions, and brain volume loss) showed significantly improved outcomes compared with placebo ($P < 0.001$ for all comparisons at 24 months). Patients in both fingolimod treatment groups had significantly fewer Gd-enhancing lesions compared with placebo at 6, 12, and 24 months and fewer new or enlarged T2-weighted lesions at 24 months. In the fingolimod groups, the median volume of T2-weighted lesions decreased between baseline and month 24 but increased with placebo. Furthermore, changes in the volume of T1 hypointense lesions favored both doses of fingolimod compared with placebo, and reductions in brain volume were less with fingolimod.[124]

In the TRANSFORMS trial, patients were randomized to receive either fingolimod 0.5 mg, 1.25 mg, or SC IFN beta-1a 30 μg/weekly. MRI outcomes showed that patients in the 2 fingolimod groups had significantly fewer new or enlarged hyperintense lesions on T2-weighted images and Gd-enhancing lesions on T1-weighted images at 12 months compared with the IFN group. In the fingolimod treatment groups, the mean percent reduction in brain volume from baseline to 12 months was significantly lower than the IFN group. However, changes in the volume of lesions on noncontrast T2- or T1-weighted images at 12 months did not differ significantly between treatment groups. Over 80% of patients in both fingolimod groups were relapse free at 12 months with reduced MRI disease activity.[125]

THE INDIVIDUAL PATIENT

MRI results from therapeutic clinical trials, such as the efficacy of an IFN beta preparation, represent treatment responses across a population of MS patients and presumably can be extrapolated to all *similar* MS patients.[5] Although this tends to be the trend if a trial is large and well-conducted with sufficient power to detect meaningful differences, results of therapy in the individual patient may not be concordant.

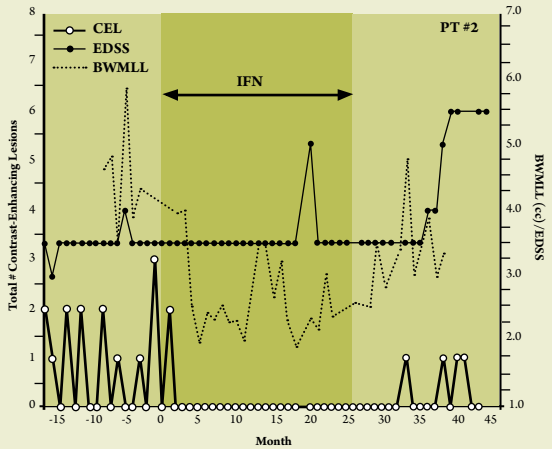
Clinicians must focus on the response of the individual patient.[5] For everyday management, identifying the responder, partial responder, and nonresponder to DMTs is essential to make treatment protocol decisions. Considering the partial efficacy of DMTs in MS and the relatively weak correlations between some MRI metrics and disability, treatment decisions should not be based on MRI alone[126] but rather should be combined with clinical assessments (discussed further).

With regard to the use of MRI in patient monitoring, T2 BOD provides a measure of total disease burden over time.[5] However, measuring the increase in new T2 lesions and/or Gd-enhancing lesions is simpler and more readily usable in everyday practice to monitor response to DMT in the individual patient (**Table 14**).[2,22,37] Counting new T2

TABLE 14: MRI Variables With Proven Utility for Monitoring Treatment Effects in MS[37]

MRI Variable	Pathophysiologic Information Provided	MS Phase/Type to be Used in	Utility for Clinical Practice
Gd-enhancing lesions	Acute area of focal inflammation	CIS, RRMS, SPMS, PPMS?	Yes
New T2 lesions	New area of tissue damage	CIS, RRMS, SPMS, PPMS?	Yes
Enlarging T2 lesions	Enlarging area of tissue damage	RRMS, SPMS	No
T1 lesions (black holes)	Lesion with marked tissue damage	RRMS, SPMS	?
T2 lesion load	Total area of clearly abnormal brain tissue	CIS, RRMS, SPMS?	No
T1 lesion load	Total area of marked tissue destruction	RRMS, SPMS?	No
Brain atrophy/volume measures	Changes in brain volume due to several factors	CIS, RRMS, SPMS, PPMS	No

FIGURE 10: Following MRI in the Clinic[127]



Following MRI in the clinic? Following the response to therapy may be limited to annual MRI to detect activity trends. In this optimal monthly MRI follow-up, responsiveness to initiation of therapy with interferon beta is apparent, as is a return toward baseline activity with cessation of therapy. Because monthly MRI is not practical, counting new T2 lesions over a 1-year interval (not shown) provides a good estimate of intercurrent MRI activity; most new lesions leave a permanent residue—the footprint of previous activity. Enhancing lesions provide estimates of activity trends and a measure of inflammation around the time of the MRI.
BWMLL=bulk white matter lesion load; CEL=contrast-enhancing lesion

hyperintense lesions over time (as a measure of interval change) and counting Gd-enhancing lesions at the time of repeat MRI (as a measure of inflammation) is an effective method. As an example, clinical monitoring of one RRMS patient receiving SC IFN beta-1b is shown in **Figure 10**.[127] The accumulation of new T2 hyperintense lesions and/or the occurrence of enhancing lesions at the time of MRI evaluation strongly suggest insufficient suppression of the inflammatory or demyelinating process, whereas the absence of these changes suggests that DMT is exerting its anticipated biological effect.[29,37]

In patients with SPMS, disability often progresses slowly and usually in the absence of new T2 or enhancing lesions. Monitoring may be less beneficial than in RRMS.[11]

In most clinical situations, monthly scans (as shown in Figure 10) are impractical or not feasible. Many specialists recommend performing an MRI one year after starting DMT to help assess treatment response. With increasing availability of DMT options and therapeutic regimens, it is likely that clinicians will expect a lower threshold for acceptable clinical and MRI disease activity, Some clinicians may choose to empirically scan patients even after 2-4 years of clinical stability to assess for silent MS lesions. However, current imaging guidelines from CMSC direct clinicians away from routine follow-up scans.[12]

It should be emphasized that there are no clear MRI methods to assess a suboptimal response to DMT; that is, specific data regarding the number of increasing new lesions reflecting suboptimal response or treatment failure are lacking. As a benchmark and because DMTs are only partially effective, knowledge of the expected accrual of new lesions over time in patients receiving DMT might be helpful. Regarding new T2 lesions, one large trial with IFN beta-1a showed accumulation of 1-2 new lesions/year in RRMS patients treated with IFN beta-1a compared with 4-5 new lesions in the placebo group.[66,128] This suggests that a suboptimal response could be considered in those with 2 or more lesions gained per year. Another interpretation of results from this trial for application to clinical monitoring is that an increase in T2 lesions of no more than 3%-4% from baseline during the first year of therapy and no more than 6%-8% over the first 2 years would indicate a favorable response to therapy.[5] Those patients with larger increases (6%-8% over 1 year, 12%-16% over 2 years) might be defined as partial or acceptable responders. However, those with higher percentage increases in lesion numbers might be considered suboptimal responders or treatment failures[5] and require a change in therapy. Similar guide posts could be developed and considered when assessing responses for all the licensed DMTs based on the results of their respective controlled trials.

T1 Hypointense Lesions

As discussed, T1 black hole formation is indicative of more severe tissue injury including axonal loss. Given the relatively good correlation between the occurrence of black holes and disability in many studies, formation of new and/or enlarging T1 hypointense lesions on an MRI evaluation suggests disease progression and a suboptimal response to therapy. A problem with monitoring this parameter is the difficulty in determining true T1 hypointensity; this is influenced greatly by the type of imaging sequence used.[37] The variability and relatively low proportion of T1 black holes among T2 lesions also limits the use of black-hole monitoring in the routine clinical setting.[37]

Primary Progressive MS

Compared with RRMS and SPMS, findings on cMRI in PPMS are similar and often indistinguishable but disease activity is lower.[21] New and enhancing lesions are fewer, the

latter related to less intense inflammation, whereas progressive disability often is related to more severe spinal cord pathology.[29,129] Increases in T2 BOD in PPMS appear related to the expansion of pre-existing lesions as opposed to the development of additional lesions.[11,29] Despite a usually lower T2 BOD relative to RRMS and SPMS, T2 lesion measures, often accompanied by brain atrophy measurements, remain the primary monitoring measure in clinical trials.[29]

There is no unequivocally effective treatment that can slow progression of PPMS.[129] A variable reduction in T2 lesion volume, T1 hypointense lesions, and T2 hypointense lesions has been observed in small studies with IFN beta therapy, but there was no effect on brain or spinal cord atrophy; no significant benefit on the development of disability was noted in these studies.[129] Similar results were seen in the large trial of glatiramer acetate in PPMS. The efficacy of fingolimod vs placebo is being studied in patients with PPMS.[130]

CLINICAL AND MRI FINDINGS IN SUBOPTIMAL RESPONSES

As mentioned, both clinical assessment and MRI are indicated when evaluating MS therapy and suboptimal response. Assessment includes incorporating MRI findings with disability and relapse rates. **Table 15**[102,126,128,131,132] presents some attributes found during an assessment that are suggestive of a suboptimal response to DMT in patients with relapsing MS. Each recommendation is separate and was generated from a consensus of opinions and recommendations from experts and working groups,[102,126,128,131,132] which included the International Working Group for Treatment Optimization in MS, the Canadian MS Working Group, and a group of neurologists from 16 MS centers in the United States.

As indicated in Table 15, MRI monitoring includes the use of new and enhancing lesions and T1 black holes. A caveat is that most of these criteria for suboptimal response have not been prospectively evaluated or validated. The varied opinions of what constitutes a suboptimal response also highlight the need for a more standardized assessment method of therapeutic response in clinical practice.

Some reasons for suboptimal response include the development of neutralizing antibodies to IFN beta, nonadherence to therapy, aggressive disease course due to only partial effectiveness of DMTs, or individual unresponsiveness to the chosen DMT.

TABLE 15: Clinical and MRI Findings Suggestive of a Suboptimal Response to DMT[102,126,128,131,132]

Essentials:

- A baseline brain MRI is indicated in all patients, including FLAIR sequences and T1/post-contrast T1 sequences
- The minimum duration of therapy required before assessing suboptimal response is 6-12 months

Findings Suggestive of a Suboptimal Response:

- Attack (relapse) rate of > 1/year or no decrease in rate after 6-12 months of DMT
- Increased attack rate compared with the rate prior to DMT
- Multiple attacks while on DMT, with cumulative residual abnormalities > 6 months
- Increasing T2 lesion load (greater than 2 lesions/year)
- Gd-enhancing lesions (greater than 2/year)
- Enhancing lesion on single scan 6 months after starting treatment (possibly sooner with IFN beta or natalizumab)
- EDSS increase of > 1 point confirmed over 6 months
- Incomplete attack recovery (particularly with increase in EDSS)
- Brainstem or spinal cord lesions that are new or recurrent
- Polyregional disease (multiple neurologic systems)
- Motor or cognitive impairment that is progressive and disrupts daily activities
- Changes in ability to perform daily activities with MRI evidence of substantial changes in T2 lesion load, parenchymal atrophy, or Gd-enhancing lesions in patients with progressive functional impairment and evidence of subtle relapse activity
- Adverse effects that are therapy limiting
- A change in MRI status (from previous MRI) in more than 3 of the following:
  - New Gd-enhancing lesions
  - New T2-weighted lesions
  - Enlarging T2 lesions
  - New hypointense T1-weighted lesions
  - Enlarging T1-hypointense lesions

Treatment of suboptimal responders might include increasing doses of first-line DMTs; switching first-line agents; changing therapy to second-line agents, such as mitoxantrone or natalizumab; considering induction escalation or combination drug regimens; enrolling in a therapeutic trial of a novel agent; or considering therapy not FDA approved for the indication of MS.

7 PRACTICAL CONSIDERATIONS IN THE USE OF CONVENTIONAL *MRI*

STANDARDIZED IMAGING PROTOCOL

Until recently, there has been no standardized protocol for how to best use cMRI in the clinical management of MS. Specifically, there was a need for consensus-based recommendations on the types of sequences and when they should be used, acquisition methods, and follow-up scans that can be used for each patient.

CMSC has developed consensus guidelines and recommendations for a standardized MRI protocol, emphasizing conventional techniques to be used in the diagnosis and follow-up of MS patients. These guidelines originally were developed in 2001 and subsequently revised in 2003, 2006, and 2009 (**Table 16**).[11,133] A similar set of guidelines have been developed by the European Federation of Neurological Societies (EFNS) Expert Panel of Neuroimaging of MS, discussing the use of conventional and nonconventional methods.[10]

The CMSC protocol initially was based on a meeting of an international group of neurologists and radiologists. Refinements of the original protocol were developed at neurological and radiological meetings in several countries over the ensuing years.[11] Following are the highlights of this protocol for use in daily clinical practice.

CMSC Guidelines for Diagnosis and Follow-up

In 2009, CMSC published revised guidelines for MRI imag-

TABLE 16: CMSC MRI Protocol Overview[133]

2003	2006	2009
Field Strength: **Brain** **1.0 T** or higher recommended (note 1T open ring) **brain spinal cord** magnets have field strength of approx .7 T and are only recommended if patients cannot tolerate closed magnet **Slices:** < 3 mm and no gap of plane resolution of < 1 mm for brain and spinal cord. < 5 mm of no gap is acceptable for brain if centers are unable to acquire 3 mm slices in allotted time	**Field Strength:** **1.0 T** or higher recommended	**Field Strength:** No specific recommendation **Brain and Spinal Cord:** Scans should be good quality with adequate signal noise ratio in pixel resolution of ≤ 1 mm x 1 mm
Sequences: 1st: Sagittal FLAIR 2nd: Axial PD/T2 3rd: Axial FLAIR 4th: Gd-enhanced T1 (if suspicious lesions on FLAIR)	**Sequences**: 1st: 3 plane (or other scout) 2nd: Sagittal fast FLAIR 3rd: Axial FSE PD/T2 4th: Axial fast FLAIR 5th: Axial pre-Gd T1 (optional) 6th: 3D T1 (optional) 7th: Axial Gd-enhanced T1	**Sequences:** 1st: Sagittal FLAIR 2nd: Axial FLAIR 3rd: Axial T2 4th: Axial T1 pre- and post-Gd
Spine Sequences 1st: Sagittal PD/T2 2nd: Sagittal pre-Gd T1 3rd: Sagittal post-Gd T1 4th: Axial post-Gd T1 through suspicious lesions 5th: Axial T2 through suspicious lesions	**Spine Sequences** 1st: 3 plane (or other scout) 2nd: Post-contrast sagittal T1 3rd: Post-contrast sagittal FSE PD/T2 4th: Post-contrast axial T1 5th: Post-contrast axial FSE PD/T2 6th: Post-contrast 3D T1 Main presenting symptoms at level of spinal cord and unresolved; if brain results are equivocal.	**Spine Sequences** 1st: Cervical cord coverage 2nd: Sagittal T2 3rd: Sagittal PD or STIR 4th: Sagittal T1

TABLE 17: Revised CMSC MRI Protocols for Brain and Spinal Cord[12]

Field strength	No specific recommendations on magnet size or strength Scans should be of good quality, with adequate signal noise ratio and resolution (in slice pixel resolution of ≤ 1 mm x 1 mm)
Slice thickness and gap	≤ 3 mm, no gap for brain and spinal cord, except ≤ 4 mm, no gap for axial spinal cord
Core brain MRI sequences	Sagittal FLAIR Axial FLAIR Axial T2 Axial T1 pre- and post-Gd
Gadolinium	Single dose 0.1 mmol/kg given over 30 seconds Minimum 5-minute delay before obtaining post-Gd T1 One of the other sequences (eg, FLAIR, T2) can be acquired during the 5-min post-Gd delay
Options for brain MRI	Axial proton density 3D IR prepared T1 gradient echo (1.0-1.5 mm thickness)
Brain MRI scan Prescription and coverage	Whole brain coverage Use subcallosal plane on sagittal localizer to prescribe the axial slices
Core spinal cord MRI sequences	Cervical cord coverage Sagittal T2 Sagittal PD or STIR Sagittal T1
Options for spinal cord MRI	Post-Gd T1 3D IR prepared T1 gradient echo (1.0-1.5 mm thickness) Thoracic cord and conus coverage Gd does not need to be given for a spinal cord MRI if it follows a contrast brain MRI study

ing in the diagnosis and follow-up of MS (**Table 17**).[12] In summary, they specify:

Patients With a CIS and Suspected MS

The baseline evaluation recommendation is a brain MRI with Gd and a spinal cord MRI if presenting symptoms or signs are at the level of the spinal cord. If there is persisting uncertainty of the diagnosis and/or the findings on brain MRI are equivocal, the recommendation is for follow-up brain MRI with Gd evaluation to assess for any new disease activity.

Patients With an Established Diagnosis of MS

The baseline evaluation recommendation is for a brain MRI with Gd for the follow-up of MS patients to: 1) evaluate an unexpected clinical worsening concerning for a secondary diagnosis, 2) reassess the original diagnosis, 3) reassess disease status before starting or modifying therapy, and 4) assess subclinical disease activity. The MRI should be considered every 1-2 years; however, the exact frequency may vary depending on clinical course and other clinical features.

A spinal cord MRI with Gd is advised for the follow-up of MS patients with clinical evidence of disease activity related to the spinal cord and in those who do not have MRI evidence of disease activity in the brain.[12]

The 2009 CMSC guidelines recommend that the radiology report contain a description of MRI findings, including lesion number, location, size, shape, and character; qualitative assessment of brain atrophy; overall T2 and T1 hypointense lesion burden; severity; comparison with previous scans for new lesion activity and atrophy; whether MRI DIS criteria are met (with specific advice to avoid statements like "McDonald diagnostic criteria met"); whether MRI DIT criteria are met; interpretation (typical, atypical, or not MS); and differential diagnosis if appropriate. MRI studies should be retained permanently by the center or hospital and be available. A "personal MRI file" also is suggested for the patient, possibly via CD, to ensure availability of scans for comparison.[12]

In 2009, CMSC also made recommendations for archival and storage. These recommendations include that copies of MRI studies be stored in a standard readable format, retained permanently, and available to medical personnel. They also suggest that patients keep their own studies on portable digital media.[12]

ADDITIONAL MRI ISSUES OF IMPORTANCE TO CLINICIANS

Some issues in the CMSC recommendations—and other areas relating to the proper use of MRI—require elaboration, as they are either frequent questions in daily clinical practice or necessary information for clinicians who manage MS patients.

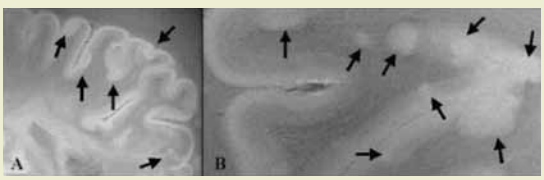
Magnetic Field Strength

Field strengths higher than 1.5 T increasingly are available for all MRI applications.[134] The rationale is that high field-strength systems, such as the 3 T field strength approved for and typically used in MS patients, provide a higher signal-intensity-to-noise ratio (SNR) for similar scan times, allowing thinner sections and higher resolution matrices that can improve lesion detection in MS patients.[2,11,23,30] Consistent with this trend, the new CMSC 2009 guidelines do not specify magnet size or strength, but reinforce that scans should be of good quality with adequate SNR and resolution (in slice pixel resolution of < 1mm x 1mm).[12]

In a review of studies comparing 1.5 T or lower field strengths with 3 T field strengths, Fillipi and Rocca[23] concluded that 3 T systems enabled detection of a higher number of lesions on both T2-weighted and post-contrast T1-weighted images, with superior between-observer agreement and a higher lesion volume. Compared with a 1.5 T system, lesion counts have been 45% higher on a 4 T system; delineation of tissue heterogeneity within lesions has been superior with 4 T.[4] The higher resolution with higher field strengths also may improve detection of cortical lesions.[2,22] Ultra-high field strengths have demonstrated lesions not visible with standard 1.0-3.0 T imaging (**Figure 11**).[9,41]

An inherent disadvantage of using higher strengths is that susceptibility effects, such as local distortions, are amplified.[134] Susceptibility-induced signal intensity loss and distortion near the base of the skull, air sinuses, and spinal cord surfaces have been seen in many cases.[2,30]

FIGURE 11: 8.0 T Visualization of Cortical Lesions[41]



Sagittal magnetic resonance images acquired at 8 T, which show multiple cortical lesions (arrows) usually not evident at 1.5 T, in a patient with MS (B is a magnification of a portion of image A)

For routine clinical practice, a 1.5 T or 3 T appears safe[135,136] and adequate. Further studies are needed to compare the higher systems to determine if they can uncover more pathology when routine imaging sequences are utilized. It is yet to be determined whether 3 T imaging at the time of a CIS could yield results that might dictate a change in DIS criteria.[11]

With the role of serial imaging becoming an integral part of monitoring disease progression, professionals should be mindful when comparing images. Lesions may not have appeared on previous scans using a less powerful magnet; however, reviewing the results of an improved technology, such as 3 T, does not necessarily indicate a new lesion.

Safety of MRI and Higher Field Strengths

Although most MRI systems operate between 0.2 and 3 T, more than 200 systems currently operate with a static magnetic field strength of 3 T or greater; a few operate at 7 T or higher.[136] These higher field-strength systems generally are reserved for research. The FDA has indicated that clinical MRI systems using a static magnetic field of up to 8 T does not pose a significant risk for patients.[136] A review of clinical studies in the literature reveals no evidence of short- or long-term adverse biological effects from static magnetic fields in humans and animals, including those up to 8 T.[135,136] However, well-controlled studies in this area are lacking. At present, use of systems > 8 T in the research setting requires informed consent and approval by an institutional review board.[136]

Biologic effects of exposure to the RF field also have been investigated. Most of the RF power for MRI is transformed into heat within patient tissues.[136] Available studies have shown only mild temperature elevations with non-significant physiological alterations during MRI with relatively high specific absorption rates (SARs).[136-138] The SAR is used to define absorption of RF radiation; it is the mass normalized rate by which RF power radiation is coupled to biologic tissue (watts/kg). Very high, whole-body SARs (6.0 watts/kg) have been physiologically tolerated in human subjects.[137]

High-field MRI (3 T or higher) generates substantially higher RF power depositions than 1.5 T. In general,

doubling of the field strength (eg, 1.5 T to 3 T) will result in a 4-fold increase in RF-power deposition for a given MRI sequence.[136] In a study evaluating procedure-related heating in the presence of a high field strength (8 T), no significant physiologic effects were observed; mild elevation of body temperature and a significant rise in skin temperature were noted, however.[138]

Varying degrees of acoustic noise are associated with MRI procedures, which can affect the patient and health care workers. Although this noise is only an annoyance to some, it has resulted occasionally in heightened anxiety and temporary or permanent hearing impairment.[136] Greater anxiety may be seen in the elderly and patients with pre-existing psychiatric disorders. The highest acoustic noise levels occur with fast gradient-echo, FSE, and echo-planar pulse sequences.[136] The use of disposable earplugs or commercially available headphones are indicated for patients undergoing MRI and should be considered for staff members and other health care workers exposed to louder MRI systems.[136]

Dose of Gd

Currently available Gd-contrast agents include gadopentetate dimeglumine, gadodiamide, gadobenate dimeglumine, gadoteridol, and gadoversetamide. With the exception of gadobenate dimeglumine, all of these agents produce similar enhancement.[30] In equal doses, gadobenate dimeglumine generally produces greater enhancement related to its increased plasma protein binding, hepatobiliary excretion (in addition to renal excretion), and overall increased relaxivity.[30]

Usual doses of Gd contrast media are 0.1 mmol/kg, with a delay of 5-10 minutes before start of the scan.[30] As previously discussed, the number of enhancing lesions and lesion contrast are increased with tripling of the usual contrast doses (eg, to 0.3 mmol/kg); this dose also may reveal more patients with enhancing lesions. Lesions in PPMS, which are fewer than in relapsing MS, may be identified more easily with higher contrast doses.[30] Compared with lesions detected by usual 0.1 mmol/kg doses, those observed only after high doses typically are smaller and may have less destructive pathology.[29,30] Optimally, triple-dose delayed imaging would follow imaging with the standard dose, thus enabling detection of lesions that enhance only with the higher dose. However, cost and time for this sequence are considerations.

Despite potential imaging advantages of triple doses, many neurologists do not advocate their routine use in clinical practice, as they do not alter diagnostic accuracy in most cases and are more costly. Higher doses also may increase the risk of nephrogenic systemic fibrosis in patients with any degree of renal impairment (below). Triple-dose Gd contrast may be useful in selected patients with ambiguous MRI findings after usual doses, but this likely will be a rare occurrence. The CMSC protocol recommends adherence to the standard 0.1 mmol/kg dose.[11]

Toxicity of Free Gd Ion (Gd^{+3}) and Gd-Based Contrast Agents

Nephrogenic Systemic Fibrosis (NSF)

An increasing number of cases of NSF have been associated with the use of Gd-based contrast agents.[139-141] This life-threatening disorder, also referred to as nephrogenic fibrosing dermopathy, is a scleroderma-like disorder with a progressive clinical course and may be fatal. A review by Mendoza and associates[142] has a more detailed discussion of its clinical and laboratory characteristics.

As of December 2009, the FDA had received reports of approximately 600 cases of NSF postexposure to Gd-based contrast media.[143] Pertinent aspects of the FDA Alert to health care professionals are shown in **Table 18**, page 36,[139] which contains warnings and recommendations based on a review of available clinical data. A boxed warning has been added to product data for all 5 Gd-based contrast agents in the United States. These warnings are based on evidence that NSF has been seen only with use of Gd-based contrast agents in patients with severe renal impairment or those with other renal insufficiency related to hepatorenal syndrome or in the peri-operative liver transplantation period.[139]

As of December 2010, the FDA required new warnings on the labels of Gd-containing contrast agents regarding the risk of NSF in patients with renal disease and emphasized the need to screen patients to detect these types of kidney dysfunction before administration. Gadofosveset trisodium, gadopentetate dimeglumine, gadodiamide, and gadoversetamide injection have been associated with increased risk and now are contraindicated for patients with acute renal injury or those with chronic severe renal disease.[144,145] Although most cases have occurred with use of gadodiamide, other agents also have been implicated.

TABLE 18: FDA Alert: Gd-Based Contrast Agents (Updated May 23, 2007)[139]

The FDA has requested manufacturers of all Gd-based contrast agents (GBCAs) to add a new boxed warning and new warnings about nephrogenic systemic fibrosis (NSF).

A new boxed warning and new warnings section describe NSF, populations at risk for NSF, and advise on screening procedures, dosing, and other considerations

Boxed Warning:

- Exposure to GBCAs increases the risk for NSF in patients with:
  - Acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73 m^2) or
  - Acute renal insufficiency of any severity due to the hepatorenal syndrome or in the peri-operative liver transplantation period.
- NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs.
- Avoid use of GBCAs unless the diagnostic information is essential and not available with noncontrast MRI.
- Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
- When administering a GBCA, do not exceed the dose recommended in product labeling. Allow sufficient time for elimination of the GBCA prior to any re-administration.

Additional New Warnings:

- Among the factors that may increase the risk for NSF are repeated or higher-than-recommended doses of a GBCA.
- For patients receiving hemodialysis, health care professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if hemodialysis prevents NSF.
- Determine the renal function of patients by obtaining a medical history or conducting laboratory tests that measure renal function prior to using a GBCA.
- The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.
- Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was Omniscan, followed by Magnevist and OptiMARK. NSF also has developed following the sequential administration of Omniscan and MultiHance and Omniscan and ProHance. The distribution of the number of reports for the individual GBCAs may relate to multiple factors, including more limited use of some GBCAs, under-reporting of NSF, characteristics of the agent, and a lack of patients' complete GBCA exposure history.

Recommendations and Considerations for Health Care Professionals:

- Become familiar with the patient populations who have a known risk for NSF. To date, NSF only has been identified in patients with:
  - Acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73 m^2) or
  - Acute renal dysfunction due to the hepatorenal syndrome or in the peri-operative liver transplantation period.
- Avoid using a GBCA in patients with known risks for developing NSF unless the diagnostic information is essential and cannot be obtained with noncontrast MRI or other diagnostic procedures.
- Prior to administering a GBCA, evaluate patients for renal dysfunction by assessing their renal function, either by obtaining a medical history or conducting a laboratory test that measures renal function.
- When administering a GBCA, do not exceed the recommended GBCA dose in product labeling and allow a sufficient period of time for elimination of the agent from the body prior to any GBCA re-administration. The elimination characteristics of each GBCA are described in the product label for each GBCA.
- For patients receiving hemodialysis, consider prompt hemodialysis after administration of a GBCA. Published data indicate that hemodialysis enhances GBCA elimination. From the first to the third hemodialysis session, reported average GBCA clearance rates were 78%, 96%, and 99%, respectively. Whether hemodialysis prevents NSF is unknown.
- Report possible cases of NSF to the FDA through the FDA's MedWatch program.

Dissociation of free Gd has been postulated as the cause of NSF in these patients (see below). However, further investigations are needed to assess the precise mechanism(s) of pathogenesis.[141]

Adverse Effects of Gd-Based Agents

Aside from the risk of NSF, Gd-based contrast agents generally are well-tolerated in both adults and children. Adverse effects have occurred in < 5% of patients based on clinical studies[146-149] and manufacturer product information. The reported frequency of adverse effects has been lowest in manufacturer data (eg, < 1% or < 2%). The most common adverse effects are nausea; headache; dizziness; vomiting; taste perversion; and injection-site symptoms, such as irritation, burning, or a cool sensation. Transient elevations of serum iron and/or serum bilirubin, without sequelae, have been observed in some patients. The frequency and nature of adverse effects is similar with all 5 agents available in the United States.[148-150] Prior adverse reactions to Gd-containing contrast media or iodinated contrast media and a history of

asthma or allergies are the primary risk factors for adverse effects with all agents.[147]

Severe reactions to Gd-based agents have been rare, and many of these occurred in patients with underlying predisposition, such as asthma or a history of allergic phenomena. Some severe events have included dyspnea, hypotension, urticaria, and anaphylactoid reactions.[146,147,150,151] Seizures have been observed in a few cases,[146,149] mainly in patients with a history of or susceptibility to seizures. The incidence of anaphylactoid reactions is somewhere between 1:100,000 and 1:500,000.[149,151]

Recent reports have described the worsening of renal function with use of Gd-containing agents in patients with pre-existing renal impairment, particularly those with diabetic nephropathy and heart failure.[152,153] These studies contrast with data from others, which have shown the relative safety of Gd contrast agents in renal insufficiency.[141,152] However, these recent reports, and the recent association with NSF, suggest that the best course is avoidance of Gd-based agents in any patient with severe renal impairment, as well as potential avoidance (especially triple doses) in lesser degrees of renal impairment.

Gd^{+3} Toxicity

Gd^{+3} is toxic,[149] which raises concerns of systemic toxicity related to its dissociation from the chelate complex. It is a relatively potent calcium-channel blocker and can block voltage-gated calcium channels.[154] In animal studies, administration of Gd in ionic form has been associated with respiratory depression/arrest, cardiovascular arrest, and hepatic necrosis.[146]

Although Gd binding to its ligand creates a thermodynamically and kinetically stable chelate complex with minimal or no metabolism after IV injection, some Gd release does occur.[141,154] The rises in plasma bilirubin and iron, which peak 2-4 hours postinjection of some available Gd chelates, has been speculated to result from Gd release immediately after injection, which produces a mild transient hemolysis.[148] These effects do not occur with all chelates, presumably related to differences in chelate stability.[148]

Dissociation of Gd from the chelate complex has been attributed to this lack of complete chelate stability, as well as the presence of other molecules competing with Gd for chelate, and any situation that causes chelate to remain in the body for a prolonged period of time.[141,149,154] Evidence suggests that transmetallation is a primary mechanism of Gd release, which occurs by displacement of Gd by other endogenous metals, such as zinc, copper, calcium, and/or iron.[146,154]

Studies assessing Gd levels and accumulation in humans after IV doses are sparse. Retention of Gd in bone has been observed in healthy patients postexposure to clinically acceptable doses of Gd-based contrast agents.[141] The effects of releasing Gd from bone over time are unknown. Gd-based contrast agents are rapidly excreted via glomerular filtration after IV doses in patients with normal renal function, but clearance is prolonged significantly in those with renal impairment; as discussed previously, this may facilitate dissociation of Gd from its ligand.[141,154] The potential for accumulation of Gd in patients with renal insufficiency and recent study findings have fueled controversy surrounding the role of free Gd in the etiology of NSF. Recent studies have shown the presence of Gd-containing deposits in paraffin-embedded tissues from patients with NSF[155] and high concentrations of Gd in tissue biopsied for up to 3 years after exposure to Gd contrast for MRI.[154] In these studies, Gd in tissues was complexed with numerous elements, including calcium, sodium, and iron—making a strong argument for transmetallation. However, other studies have found no evidence of transmetallation or metabolism of Gd in patients with severe renal insufficiency or in those who are undergoing hemodialysis following administration of Gd-contrast agents.[141]

At present, the role of Gd toxicity in NSF remains unclear. The low order of adverse reactions observed with Gd-contrast agents used in MRI, now extending over 25 years,[146] would suggest that the small amounts of free Gd released postinjection do not pose a serious health threat in patients without defined risk factors for NSF. However, in addition to following FDA guidelines to prevent NSF, avoidance of these agents in patients with any degree of renal impairment, especially in the presence of risk factors, should be considered.

Corticosteroids and Enhancing Lesions

High doses of corticosteroids have an almost immediate effect on suppressing Gd enhancement and last for months.[30] However, in general, clinically useful enhanced MRI still can be performed about 30 days after corticosteroid administration.[30]

Referral to a Neurologist

Due to the complexities of currently available MS therapies and MRI techniques and the need for long-term monitoring and optimization of DMT in patients presenting with symptoms suggestive of a CIS, primary care providers should consider referral to a neurologist for further evaluation and MRI studies.[77] A similar consideration is suggested for any patient with a past history suspicious for MS.

8 SOME ADVANCED MRI TECHNIQUES

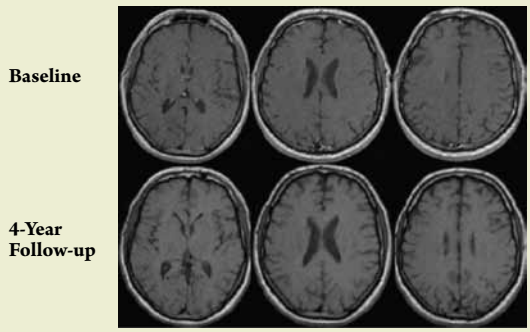
The "clinical MRI paradox" is the presence of new lesions on MRI in the absence of clinical symptoms (subclinical disease activity) and clinical progression in the absence of new MRI lesions (non-radiologic disease progression).[23] These observations, coupled with the inability of cMRI methods to adequately detect the cortical demyelination and tissue injury confirmed on a pathology exam, have led to the development of more advanced or nonconventional MRI techniques (Table 3, page 9). Due to the present impracticality of advanced techniques in the routine clinical setting, except for visual measures of brain atrophy, they have not been emphasized in this primer. For completeness, aspects of 5 advanced techniques—brain and spinal cord atrophy, magnetization transfer imaging, functional MRI (fMRI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy—are discussed briefly.

BRAIN AND SPINAL CORD ATROPHY

Considered a cMRI technique by some and an advanced technique by others, brain atrophy is an imaging hallmark in MS and provides information complementary to lesion assessments. It is an objective measure of global disease burden and an indirect measure of disease severity and progression.[2,3,29,32] Brain atrophy is found in all stages and forms of MS in a progressive manner and currently is assessed in clinical trials to monitor disease progression.

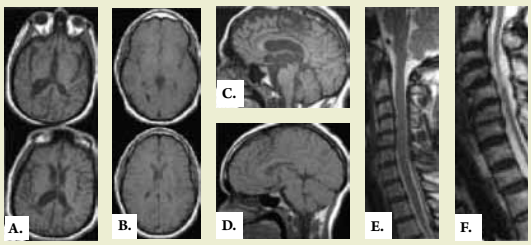
Brain atrophy can be detected early in MS, including in patients presenting with a CIS.[3,22,32] Both WM and GM are affected, and the average rate of brain volume loss in MS patients is 0.6%-1.2% per year compared with 0.1%-0.3% per year in the normal aging process of healthy individuals.[2,22]

FIGURE 12: Progressive Brain Atrophy in RRMS[22]



Progressive brain atrophy in a 41-year-old man with RRMS imaged at baseline and 4 years later. Noncontrast T1-weighted images show progressive enlargement of the ventricles and subarachnoid spaces consistent with diffuse brain volume loss.

FIGURE 13: Brain Atrophy in SPMS[3]



Axial T1-weighted images (A,B) showing brain atrophy in a 30-year-old man with secondary progressive MS (A) with moderate to severe cerebral atrophy compared with normal age-matched healthy control (B). The T1-weighted sagittal images of the same patient (C) and age-matched control (D) show corpus callosum atrophy, a common finding in MS. T2-weighted sagittal images of a 50-year-old woman with benign relapsing-remitting MS (E) and a 57-year-old woman with secondary progressive MS (F) show spinal cord atrophy in the latter.

The rate for MS is similar for patients with RRMS, SPMS, and PPMS.[22,32] Brain atrophy over time in a 41-year-old male with MS is shown in **Figure 12**.[22] Axial and sagittal views of brain atrophy in a patient with SPMS compared with age-matched controls are shown in **Figure 13** (**A-D**).[3]

Atrophy usually is seen as enlarged ventricles and reduced size of the corpus callosum.[2] Mechanisms of atrophy remain somewhat speculative, although current thinking suggests it results from myelin and axonal loss and changes in the supporting tissue matrix.[2,11,22,34] Atrophy can be measured by simple linear measures, such as caudate width or third ventricle width, or by more advanced, semi-automated or automated measure of whole-brain atrophy.[22,32] Several

advanced, 3D measures can determine the volume of brain parenchyma relative to total intracranial volume.[32,156,157] However, more advanced methods that quantify atrophy are limited by their complexity, unfamiliarity to most clinicians, and lack of availability for routine clinical use.

In many patients, determination of atrophy can be accomplished by a direct comparison of routine MRIs acquired over time.[32,77] However, this is limited by the necessity of ensuring that the slice positions and orientations are well-matched on re-imaging.[32] In addition, considering the small rates of brain-tissue loss, it may be difficult to readily detect changes with the naked eye on annual scans.[32] These problems also have served as a barrier to obtaining routine acquisitions for assessing atrophy in the clinical setting.

Indeed, a reliable, quick, and clinician-friendly technique for routine clinical use is in strong demand.[2] The development of precise quantitative methods for measuring brain atrophy is progressing rapidly and soon may become a practical tool for the everyday practice setting. At present, assessment of brain atrophy is considered an option in the CMSC imaging guidelines.[11]

Brain atrophy correlates well with disability in MS and is a good predictor of long-term neurologic impairment and disability.[2,22,31,32] In general, the correlation between brain atrophy and disability has been stronger with use of the MS Functional Composite (MSFC) scale compared with EDSS scores,[32] although the EDSS has been used much more commonly in clinical studies. Several studies have shown that clinical disability on EDSS scores correlated significantly better with brain atrophy than lesion measurements on cMRI, including T2 hyperintense lesions and T1 hypointense lesion volumes.[22,31,158] In an 8-year longitudinal study, Fisher and colleagues[159] showed that RRMS patients with the highest rates of MRI-detected brain atrophy in the first 2 years correlated with significantly greater disability (as measured by EDSS score) at the 8-year follow-up point than patients with the lowest first 2-year rates of atrophy.

Cognitive impairment, fatigue, depression, and health-related quality of life (HRQOL) also have correlated well with brain atrophy.[160] Cognitive decline has correlated better with brain atrophy than lesion load in early RRMS.[160]

Spinal cord atrophy related to MS pathological processes also is evident on MRI. Like brain atrophy, spinal cord atrophy begins early, even before the onset of clinical symptoms.[32] More spinal cord atrophy is present in patients with SPMS relative to RRMS[32] (**Figure 13, E and F**). However, measuring spinal cord atrophy also poses a challenge; partial volume effects are significant, as the cord is very small in relation to the image resolutions typically used.[32] Estimation of cord cross-sectional area (at C2/C3) is being developed using images with a 3D, T1-weighted, fast spoiled-gradient echo acquisition.[32] Presently, however, assessing spinal cord atrophy often is not practical or accessible in routine clinical practice.

Spinal cord atrophy has correlated strongly with disability in MS despite differing methods of atrophy measurement.[31,32] Disability is uniformly higher on EDSS scores in patients with spinal cord atrophy than in those without atrophy,[22,31] and studies have shown significant spinal cord atrophy-disability correlations when there were no disability correlations with T2 hyperintense or T1 hypointense lesions.[22]

With continued development of more practically applicable technology, measurements of whole brain and spinal cord atrophy may assume a role in the monitoring of individual patients. Glatiramer acetate and IFN beta have been shown to slow progression of brain atrophy in some, but not all, placebo-controlled studies.[22,32,157] Additionally, IV methylprednisolone preserved brain volume for up to 5 years in one trial.[161]

In one trial with glatiramer acetate, whole-brain volume loss was shown to be reduced by 40% with prolonged therapy. However, when data were analyzed with a different method of estimating atrophy (7-slice method), a treatment benefit could not be detected, thus emphasizing the importance of technical factors in the use of atrophy as an outcome measure.[22]

MAGNETIZATION TRANSFER IMAGING

MTI is an advanced, quantitative MRI technique based on the interaction and magnetization exchange between mobile protons in free water with those bound to macromolecules.[22,162] In the CNS, these states correspond to protons in tissue water and those in the macromolecules of myelin and other cell membranes.[21] The protons bound to macromolecules typically are not seen on cMRI; however, they interact

with and affect the spin of the protons in free water, creating the magnetization transfer (MT) contrast effect.

Two MRI scans, usually T2 weighted, are acquired sequentially with and without the addition of an off-resonance MT pulse. These 2 images are compared, and MT ratios (MTRs) are created. The MTR is proportional to the concentration of macromolecules in myelin and cell membranes, and a low MTR is indicative of a reduced capacity of CNS macromolecules to exchange magnetization with surrounding water molecules. This reflects pathologic and/or structural tissue injury (eg, damage to myelin or the axonal membrane).[21,22,162] Very low MTRs indicate areas of severe tissue loss. There is a strong correlation between MTR values derived from MS lesions and NAWM, with the percentage of residual axons and the degree of demyelination.[2,21]

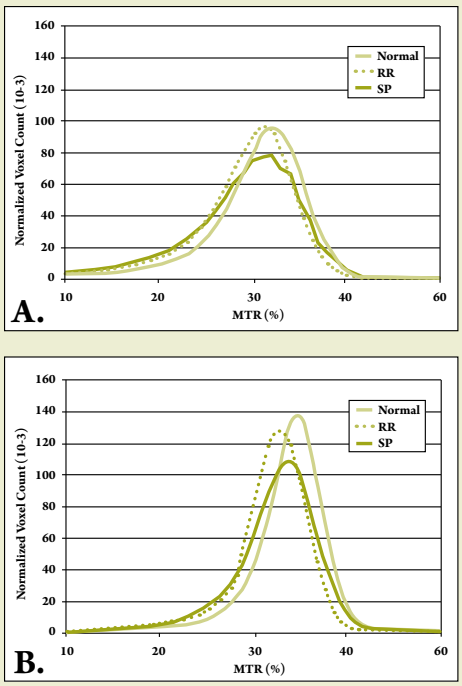
Therefore, MTI can demonstrate pathologic changes in NAWM that are undetectable on cMRI and may differentiate CNS tissue edema from demyelination.[36] Studies have shown that mean MTR values in many areas of NAWM substantially are lower in MS patients compared with controls.[2,163-165] Similar findings have been reported in normal-appearing gray matter (NAGM), optic nerves, and the cervical cord.[22,163] MTR changes are seen very early in MS[163] and can occur before the appearance of new enhancing lesions.

MTR data usually are expressed as region-of-interest or whole-brain histograms, with analysis performed on peak height, peak position, and mean MTR.[22,163,164] Patients with MS typically have lower peak height, peak position, and mean MTR than normal subjects on whole-brain histograms. Histogram parameters differ based on the form of MS, such that patients with SPMS have a greater reduction in MTR than RRMS patients (**Figure 14**).[2,164]

Decreases in MTR are predictive of disease progression in MS, such as the accumulation of disability.[22,166,167] Whole-brain MTR percentage changes over a 1-year period have been highly predictive of physical disability accumulation in the subsequent 4 years[167] and 8 years[162] in MS patients. In other studies, decreases in MTR-histogram peak height have correlated better with brain atrophy than T2 BOD.[164] Cognitive impairment in MS also has been correlated with decreases in MTR.[164]

Studies assessing MTR changes in relation to lesion evolution have shown that MTR declines several months prior

FIGURE 14: MTR Histograms: SPMS vs RRMS[2]



Averaged magnetization transfer ratio histograms from 3 groups (healthy control, RRMS, and SPMS) for global NAGM (A) and NAWM (B) tissues. Lower normalized peak height in SPMS population indicates relatively less residual normal brain tissue compared with that in RRMS patients.

to the appearance of Gd-enhancing lesions, then decreases further as enhancement occurs.[22,164] If MTR decreases are only moderate, partial or complete MTR recovery is likely, reflecting remyelination or other reparative processes. However, greater decreases in MTR at enhancement are predictive of evolution to permanent tissue loss, as shown by the development of T1 hypointense lesions.[22] Disadvantages of MTR include variability across different scanners, lack of specificity, and difficulties in accurate quantification, which have limited its use in the diagnosis of MS to date.[36]

Lesion evolution in response to DMT has been studied using MTI. In studies of newly formed lesions in RRMS patients using a baseline vs treatment design, lesion recovery on MTR after Gd enhancement has been significantly higher for lesions treated with methylprednisolone or forming in the presence of IFN beta-1a compared with untreated lesions.[21] These findings suggest a reduction in tissue damage and promotion of remyelination during

treatment. Studies of this nature are defining a role for MTI in therapeutic monitoring.

FUNCTIONAL MRI

In fMRI, changes in blood oxygen levels due to neuronal metabolism and activation causing signal changes are detected, providing information on abnormal patterns of brain activation in CNS disease. In MS patients, fMRI is used to demonstrate cortical adaptation and plasticity following CNS tissue damage and can detect abnormalities early in MS and in a CIS. fMRI studies show that brain activation is detected significantly more often in MS patients than in control subjects, and MS patients appear to recruit additional brain areas during cognitive assessments compared with controls. fMRI offers a sensitive research tool for the assessment of subtle CNS damage and adaptive functional changes in MS patients associated with movement or motor learning.[36]

DIFFUSION TENSOR IMAGING

Diffusion imaging measures the movement of water molecules resulting from thermal energy and can provide information on the orientation, integrity, size, and geometry of neural tracts in CNS tissues by assessing magnitude and directionality of water diffusion. DTI can be used in MS to assess occult and progressive tissue damage in NAWM and NAGM and also has been shown to be useful in the prediction of cognitive impairment in MS. Further developments of DTI techniques including diffusion tensor tractography can provide valuable information on mechanisms of disability development in MS patients. Studies on the ability of DTI to detect and distinguish between different demyelinating conditions and on the application of DTI to monitor disease progression in MS are required.[36]

MAGNETIC RESONANCE SPECTROSCOPY

MRS investigates alterations in the concentration of proton-containing CNS tissue metabolites in lesions and NAWM that reflect a variety of pathologic processes in MS. Through selective suppression of protons in the free-water pool, proton magnetic resonance spectroscopy (^{1}H-MRS) can sample signals from protons associated with molecules that have biologic significance.[22,53] One of the most prevalent MRS-visible compounds (ie, resonances) is N-acetylaspartate (NAA), the most concentrated metabolite in the CNS. It is contained almost exclusively within neurons and axons and is formed as a byproduct of neuronal mitochondrial metabolism.[36] Others metabolites detected on MRS include N-aspartylglutamate, creatine (Cr), phosphocreatine, choline (Cho), lactate, and mobile lipids.[21,22,34,53] Less prominent resonances include myoinositol, glutamate, and gamma-aminobutyric acid (GABA).[22]

All of these metabolite compounds are affected abnormally in MS. Summarizing briefly, a significant reduction in NAA is seen in MS lesions on ^{1}H-MRS, which is attributable to axonal dysfunction and/or axonal loss, and thus is a marker of neuronal viability.[34,53] A steady decline in the levels of NAA (4%-6% per year) has been observed in MS patients, and this correlates strongly with disability. Decreases in NAA also have been seen in NAWM adjacent to or distant from lesions.[21,36] Some studies also have shown reversibility of decreases in NAA, indicating possible recovery of mitochondrial function.[36]

Elevated peaks of Cho, lactate, and lipids are indicative of inflammation and demyelination.[4,53] Glutamate levels have been shown to be elevated in acute enhancing lesions and NAWM, which may indicate axonal damage and brain atrophy.[168] Changes in spectroscopic peaks of these compounds thus can serve as biomarkers of MS pathology. In general, Cr remains relatively constant despite MS pathology and is used for ratio determinations. A typical finding in demyelinating lesions is a decrease in the NAA:Cr ratio.[2,34] An increased Cho:Cr ratio also may be seen.

Similar to MTI, but unlike cMRI, ^{1}H-MRS can identify abnormalities in normal-appearing brain tissue prior to lesion development. When applied to clinical monitoring, a decreasing NAA:Cr ratio has correlated with disability and cognitive dysfunction, as shown in several studies.[4,21] This suggests that ^{1}H-MRS measures of brain-metabolite markers may be a better predictor of clinical disability than cMRI methods.[4,22] NAA decreases have correlated somewhat with T2 BOD, brain atrophy, and the extent of tissue damage reflected by T1 hypointense BOD.[22]

^{1}H-MRS has been used in therapeutic monitoring. Although some studies have shown benefits of IFN beta on ^{1}H-MRS metrics, such as an increase in the NAA:Cr ratio,[21,22] others have found little effect.[22] A 4-year prospective study recently

demonstrated a beneficial and sustained effect of glatiramer acetate on axonal metabolic function in RRMS patients; a 13% increase in the NAA:Cr ratio (multivoxel area of interest) was seen at year 4 relative to baseline.[169] Further well-controlled investigations are warranted to evaluate the efficacy of IFN beta and glatiramer acetate in improving axonal function.

Limitations of ^{1}H-MRS include being a time-consuming procedure; the reproducibility of measured metabolite concentrations is only modest; acquisition requires post-processing; and interpretation by experienced personnel primarily limits its clinical use to selected MS centers.[23,24,36]

9 CONCLUSION

Radiological imaging for MS is developing rapidly. All MR imaging techniques have inherent limitations, but appropriate use of cMRI can improve diagnostic accuracy in patients with suspected MS, monitor clinical status in diagnosed patients, offer sensitive and useful assessment of disease activity, and assist in determining the response to treatment. The future promises more advanced, and perhaps more sensitive, imaging techniques that offer greater insight into the pathology and mechanisms of MS as well as potentially improved tools for assessing prognosis and monitoring disease progression and clinical outcomes.

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GLOSSARY OF TERMS

Black hole – chronic T1-hypointense lesions that reflect severe demyelination, axonal loss, and matrix destruction. Correlated with the subsequent development of brain atrophy in some studies.

Brain atrophy – reflects the end result of severely damaging pathological processes seen both focally and diffusely.

Clinical MRI paradox – the presence of new lesions on MRI in the absence of clinical symptoms and clinical progress in the absence of new MRI lesions.

Conventional MRI – approaches enabling reconstruction of images for real-time viewing, which can be interpreted subjectively by an experienced clinician without the need for extensive offline data transformation, processing, or analysis.

Echo time – time between the initial 90-degree RF pulse and the echo.

FLAIR – uses an inversion pulse with a long TE, which generates heavy T2-weighted images and nulls the CSF.

Gadolinium – a chemical compound that can be administered to a person during MRI to help distinguish between new and old lesions.

Gadolinium-enhancing lesion – a lesion appearing on MRI, following injection of gadolinium, that reveals a breakdown in the BBB. This breakdown indicates either a newly active lesion or the re-activation of an old one.

Juxtacortical – adjacent to a white-matter component.

Magnetic resonance spectroscopy – investigates the alterations of tissue metabolites that reflect a variety of pathologic processes in MS.

Magnetization transfer imaging – an advanced, quantitative MRI technique based on the interaction and magnetization exchange between mobile protons in free water with those bound to macromolecules.

Magnetization transfer ratio – proportional to the concentration of macromolecules, and a low ratio is indicative of a reduced capacity of CNS macromolecules to exchange magnetization with surrounding water molecules.

Nonconventional MRI – advanced pulse sequences, beyond the basic pulses performed for T1 and T2, and typically require post-processing to analyze and display data.

Null – water appears dark instead of bright on T2-weighted scans.

Proton density – the concentration of tissue protons in the form of water and macromolecules.

Repetition time – the time between consecutive 90-degree RF pulses.

Ring-enhancing lesion – suggestive of greater tissue damage and more aggressive MS and have been shown to be strong predictors of persistent hypointense T1 lesions and subsequent development of brain atrophy.

T1 relaxation time – time required for protons to realign within the magnetic field and give up the RF energy keeping them aligned.

T1-weighted images –show acute MS lesions as hypointense areas due to edema of the damaged brain tissue. It was the first quantitative, volumetric imaging study used in MS.

T2 lesion load – total lesion number and/or volume.

T2 relaxation time – time for protons to lose their phase alignment within the original magnetic field.

T2-weighted images –show hyperintense bright lesions representing demyelination, edema, gliosis, or matrix destruction.

ABBREVIATIONS GUIDE

^{1}H-MRS	proton magnetic resonance spectroscopy
AAN	American Academy of Neurology
ADEM	acute disseminated encephalomyelitis
BBB	blood-brain barrier
AQP4	aquaporin 4
BOD	burden of disease
CDMS	clinically definite MS
Cho	choline
CIS	clinically isolated syndrome
CNS	central nervous system
cMRI	conventional MRI
CMSC	Consortium of Multiple Sclerosis Centers
Cr	creatine
CSF	cerebrospinal fluid
CT	computed tomography
DIS	dissemination in space
DIT	dissemination in time
DMT	disease-modifying therapy
DTI	diffusion tensor imaging
EDSS	expanded disability status scale
FDA	United States Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
fMRI	functional MRI
FSE	fast spin echo
GABA	gamma-aminobutyric acid
Gd	gadolinium
Gd^{+3}	free gadolinium ion
GM	gray matter
HRQOL	health-related quality of life
HVD	high-volume delayed
IFN	interferon
IgG	immunoglobulin G
IM	intramuscular
IP	international panel
IV	intravenous
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MSFC	multiple sclerosis functional composite
MT	magnetization transfer
MTI	magnetization transfer imaging
MTR	magnetization transfer ratio
NAA	N-acetylaspartate
NAGM	normal-appearing gray matter
NAWM	normal-appearing white matter
NMO	neuromyelitis optica
NMSS	National Multiple Sclerosis Society
NSF	nephrogenic systemic fibrosis
OCB	oligoclonal band
PD	proton density
PPMS	primary progressive MS
PSIR	phase sensitive inversion recovery
RF	radio-frequency
RIS	radiologically isolated syndrome
RRMS	relapsing-remitting MS
SAR	specific absorption rate
SC	subcutaneous
SE	spin echo
SNR	signal intensity to noise
SPMS	secondary progressive MS
STIR	short-tau inversion recovery
T	Tesla
TE	echo time
TR	repetition time
VEP	visual evoked potentials
WM	white matter

POSTTEST

1. **At present, most experts agree that conventional MRI is composed of:**
   a. Noncontrast T1-weighted images, Gd-enhanced T1 images, and brain atrophy assessments
   b. T2-weighted images, noncontrast T1-weighted images, and magnetic resonance spectroscopy
   c. T2-weighted images, Gd-enhanced T1 images, and noncontrast T1-weighted images
   d. T2-weighted images, Gd-enhanced T1 images, noncontrast T1-weighted images, and brain atrophy assessments
   e. None of these are correct

2. **Although conventional MRI techniques alone are useful for assessing clinical status and response to therapeutic agents in MS, they are not sufficiently useful to aid in the diagnosis of the disease.**
   a. True
   b. False

3. **Which of the following is *false* regarding MS pathology as seen by conventional MRI:**
   a. Enhancing lesions are the first detectable event on conventional MRI reflecting disruption and permeability of the BBB.
   b. T2-weighted images are highly sensitive to lesion detection in both white and deep gray matter, but T2 hyperintensities are nonspecific with regard to underlying pathology.
   c. Approximately one-third of acute T1 hypointense lesions do not return to isointensity over time (chronic T1 hypointense lesions) and are known as black holes, representing severe demyelination, axonal loss, and matrix destruction.
   d. Black holes occur in more advanced disease and are not seen in early MS.
   e. In some patients with MS (about 25%), T2 hyperintense lesions may be seen only in the spinal cord.

4. **For the diagnosis of MS:**
   a. The Swanton criteria and the 2005 McDonald criteria have demonstrated similar specificity and each can provide a reliable diagnosis in patients with a CIS; however, prospective studies are needed before Swanton criteria can be recommended routinely.
   b. The 2005 McDonald criteria are recommended for most patients; however, the AAN criteria can be considered for those presenting with a highly characteristic CIS.
   c. Two clinical relapses over time with no other identifiable causes may constitute a diagnosis of MS, even in the absence of MRI or CSF findings.
   d. Use of more relaxed criteria, such as those advanced by the AAN, increases the risk of a false-positive diagnosis.
   e. All of the above are correct.

5. **The burden of chronic T1 hypointensities (T1 BOD) has correlated with brain atrophy in some studies and has correlated better with clinical disability than T2 hyperintense lesion burden has.**
   a. True
   b. False

6. **Assessing the therapeutic response of DMT over time in the individual patient with conventional MRI may be achieved by monitoring:**
   a. T1 BOD
   b. New T2 lesions and/or new enhancing lesions
   c. T2/T1 ratio
   d. T2 BOD
   e. New black hole formation

7. Based on the standardized MRI protocol recommended by the CMSC, follow-up MRI studies after initial scan are indicated:

a. Routinely, every 6 months
b. To reassess disease burden for the purpose of initiation of treatment
c. At least once a year
d. If there is unexpected clinical worsening or when the clinician has a concern regarding the course of the patient
e. (b) and (d) are correct

8. Which of the following is true about magnetic field strengths with use of MRI in MS?

a. For routine clinical practice, a strength of 1.5 T or 3.0 T appears safe and adequate.
b. Field strengths higher than 1.5 T provide the benefit of lower signal-intensity-to-noise ratio (SNR) for similar scan times.
c. Higher field strengths minimize susceptibility defects, such as distortions.
d. At the time of a CIS, 3.0 T imaging has yielded results that will clearly dictate a change in DIS criteria in the future.
e. (a) and (d) are true

9. Hazards of injection of Gd-based contrast agents include:

a. NSF in patients with or without renal impairment
b. A high frequency of anaphylactoid reactions (1:500)
c. Bluish skin discoloration
d. Nausea, headache, and injection-site reactions
e. Guillain-Barre syndrome

10. Which of the following is not true regarding advanced MRI techniques:

a. MTI and ^{1}H-MRS are capable of identifying abnormalities in NAWM not seen on conventional MRI.
b. Brain atrophy correlates well with clinical disability.
c. A declining NAA:Cr ratio with the use of ^{1}H-MRS has correlated with disability and cognitive dysfunction in MS patients.
d. With use of MTI, the decreases in MTR are predictive of disease progression in MS, such as the accumulation of disability.
e. All advanced techniques are now available for practical use in the routine clinical setting and should be considered as adjuncts to, or in lieu of, conventional MRI for monitoring of clinical status and response to therapy.

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Please circle the appropriate answer:

1) a b c d e	**2)** a b	**3)** a b c d e	**4)** a b c d e	**5)** a b
6) a b c d e	**7)** a b c d e	**8)** a b c d e	**9)** a b c d e	**10)** a b c d e

Please answer the following questions by circling the appropriate rating.

EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED OBJECTIVES

	Outstanding	Good	Satisfactory	Fair	Poor
Describe MR imaging protocol as presented in the most recent CMSC guideline	5	4	3	2	1
Describe how MRI is used to find spinal cord and brain lesions in MS	5	4	3	2	1
Explain the differences between T1-weighted and T2-weighted images	5	4	3	2	1
Discuss how gadolinium is used in MRI, as well as its risks	5	4	3	2	1

Please indicate if this activity was free from commercial bias. ☐ Yes ☐ No

If No, please indicate the topic(s) that were not free from commercial bias.

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity — 5 4 3 2 1
Enhanced my current knowledge base — 5 4 3 2 1
Will help me improve patient care — 5 4 3 2 1
Provided new ideas or information I expect to use — 5 4 3 2 1
Was timely and will influence my practice of medicine — 5 4 3 2 1
Addressed my most pressing questions — 5 4 3 2 1

Please indicate any changes you plan to make in your practice of medicine as a result of information you received from this activity.

Please rate your commitment level to making these changes — 5 4 3 2 1

In what time frame do you anticipate making these changes?

☐ Immediately ☐ 1-2 months ☐ 3-6 months ☐ At some point in the future

Based on my participation in this CME activity, I now will incorporate the following new clinical strategies:
(Check all that apply.)

☐ Utilize the most current information pertaining to the optimal use of MRI as it applies to MS in the clinical setting.
☐ Effectively select MRI techniques to assess CNS pathology, contribute to the diagnosis of the disease, and help monitor MS-related CNS tissue changes over time in order to preserve quality of life.
☐ Optimally use and adhere to recommended protocols regarding imaging techniques and frequency/use of imaging; use and apply these imaging findings in clinical practice.
☐ Integrate MRI findings into the assessment of treatment efficacy to optimize treatment decisions and long-term disease management.
☐ Evaluate brain and spinal cord atrophy using advanced imaging and choose to manage and monitor an individual MS
☐ I already do all of these things.

If this activity did not give you strategies to be better able to practice medicine, please list the factors acting as barriers.

This activity was designed to help the participant master the ABMS/ACGME core competency of patient care and medical knowledge. How well did this activity address this competency? — 5 4 3 2 1

Please provide general comments regarding this activity and suggest how it might be improved.

Please provide any other medical topics that would be of interest to you.