

MONITORING DISEASE PROGRESSION: INCORPORATING MRI AND NEW MODALITIES IN CLINICAL DECISION MAKING*

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ABSTRACT

The diagnostic process and the management of patients with multiple sclerosis (MS) have undergone remarkable changes over the last 2 decades with the introduction of new paraclinical measures of disease, such as imaging modalities (eg, magnetic resonance imaging [MRI]), and the use of disease-modifying therapies. This article reviews the diagnosis and monitoring of MS. Currently, MS is a clinical diagnosis supported by ancillary studies, including MRI, evaluation of cerebrospinal fluid for signs of immune activation, and evoked potentials. Other modalities, such as optical coherence tomography, are being considered for use in some centers. Because MS can have a variable presentation and course, practitioners are required to consider multiple alternative diagnoses in the evaluation of patients. The Poser criteria, published in 1983, were superseded by the recommendations of the McDonald Committee, originally published in 2001 and subsequently revised 5 years later. We discuss the potential roles that current and emerging diagnostic tests will play in the recognition of the heterogeneity of MS pathology, stratification

of the patient population for not only the diagnosis but also the type of central nervous system injury, prognostication of disease progression and severity, and how the appreciation of the evolution of these issues is affecting clinical practice.

This article emphasizes monitoring disease progression and incorporating new modalities in clinical decision making. Although clinical evidence remains central to the diagnosis of MS, MRI studies should play an increasingly important role in the everyday clinical practice of community-based practitioners. MRI studies are useful for MS diagnosis, disease monitoring, and clinical trials. In this article, we also raise questions regarding optimal MRI frequency, use of high-field-strength MRI, and the benefits and pitfalls of using imaging studies in clinical decision making, even in the absence of clinical signs and symptoms. (*Adv Stud Med.* 2008;8(8):266-273)

HISTORICAL PERSPECTIVE

The definitive diagnosis of multiple sclerosis (MS) has long been a challenge to clinicians. Today, we face the same fundamental questions faced by our peers 25 years ago; there is no reliable, specific, and sensitive laboratory test available for the diagnosis of MS.¹ The diagnosis of MS remains a clinical one and is still very much a diagnosis of exclusion.

In 2001, an international panel of physicians chaired by Ian McDonald presented what has come to be known as the McDonald criteria. These criteria placed an emphasis on the dissemination of lesions in time and space, in addition to the use of paraclinical

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testing—specifically magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) testing for oligoclonal bands and elevated immunoglobulin (Ig) G index, and visual evoked potentials (VEPs)—in order to establish a diagnosis of MS.²

The McDonald criteria allowed for 5 types of clinical presentations to establish the diagnosis of MS:

- The first clinical presentation required only that a patient have 2 or more attacks separated by time, with objective clinical evidence of 2 or more lesions.²
- The second clinical presentation consisted of a patient with 2 or more attacks separated by time and objective clinical evidence of only 1 lesion. Before a diagnosis of MS could be made, further evidence would be needed through either an MRI revealing dissemination in space (as per criteria developed by Barkhof et al and Tintore et al; Sidebar), or 2 or more MRI-detected lesions consistent with MS combined with positive CSF findings (evidence of oligoclonal banding or elevated IgG index), or by awaiting further clinical attacks implicating a different neurologic site.^{3,4}
- The third clinical presentation consisted of a patient with 1 attack and objective clinical evidence of 2 or more lesions. In order to establish a diagnosis of MS, there must also be evidence of dissemination in time, as demonstrated by MRI (additional gadolinium [Gd]-enhancing lesion found on MRI ≥ 3 months later) or a second clinical attack.
- The fourth clinical presentation consisted of a patient with 1 attack and objective clinical evidence of a single lesion. In this case, an MS diagnosis requires evidence of dissemination in space as demonstrated by MRI (Sidebar), 2 or more MRI-detected lesions consistent with MS combined with positive CSF findings and evidence of dissemination in time as demonstrated by MRI, or a second clinical attack.
- The fifth and final clinical presentation considered by McDonald et al involved a patient with insidious neurologic progression suggestive of MS (primary progressive MS [PPMS]). The additional criteria for MS diagnosis in this case required positive CSF findings combined with dissemination in space, as demonstrated by either:
 - Nine or more T2 lesions in the brain, or 2 or

more lesions in the spinal cord, or 4 to 8 brain lesions plus 1 spinal cord lesion on MRI,
or

- An abnormal VEP associated with either 4 to 8 brain lesions, or fewer than 4 brain lesions plus 1 spinal cord lesion on MRI, and dissemination in time, as demonstrated by MRI or continued progression for 1 year.²

These criteria have been validated in several studies. One study of patients with clinically isolated syndrome (CIS), and in whom a diagnosis of MS was suspected, revealed that patients who developed MS after 3 years were correctly predicted with a sensitivity and specificity of 83% and an accuracy of 83% at 1 year.⁵ Another study followed patients with CIS, in which the previous Poser diagnostic criteria predicted clinically definite MS (CDMS) in 11% of the patients, whereas the McDonald criteria predicted CDMS in 37% after 1 year. At the end of 1 year, the McDonald criteria predicted MS in patients with CIS with a sensitivity of 74%, a specificity of 86%, and an accuracy of 80%.⁶

It was recognized that the McDonald criteria would need to be revised yet again in light of new data regarding the diagnosis of MS in relation to MRI criteria. Polman et al provided a fairly thorough review of the intervening studies on diagnostic criteria. This paper concluded that many of the studies looking to quantify the sensitivity and specificity of the McDonald criteria may have suffered from several types of bias, including referral and patient filtering bias, and that the usefulness of these studies might be mitigated by the variation in duration of follow-up,

SIDEBAR. MRI CRITERIA TO ESTABLISH DISSEMINATION IN SPACE

Three of the following 4 criteria must be true:

1. One Gd-enhancing lesion or 9 T2-hyperintense lesions if there is no Gd enhancement
2. At least 1 infratentorial lesion
3. At least 1 juxtacortical lesion
4. At least 3 periventricular lesions
 - One spinal cord lesion may be substituted for 1 brain lesion

Gd = gadolinium; MRI = magnetic resonance imaging.
Data from McDonald et al²; Barkhof et al³; and Tintore et al.⁴

patient selection and inclusion, and MRI entry criteria.⁷ This review also highlighted portions of the criteria that may have been regarded as confusing or imprecise by practicing clinicians.

MCDONALD CRITERIA REVISED

The International Panel on the Diagnosis of Multiple Sclerosis reconvened nearly 5 years after the original McDonald criteria were created to incorporate new evidence and to revise previously vague concepts.

Although the panel agreed that dissemination in both time and space are essential for the diagnosis of MS, the evidence of dissemination in time might be more important than that of space.⁷ The primary revision with regard to MRI came in the consideration that temporal dissemination could be established by a Gd-enhancing lesion detected in a scan performed at least 3 months after the initial clinical event at a site different from that of the initial event or by the detection of a new T2 lesion in a scan performed at any time, using a reference scan done at least 30 days after the initial clinical event for comparison.

Thus, any new T2 lesion occurring at any point beyond 30 days after the onset of the initial clinical event may be useful in reaching the diagnostic criteria for dissemination of disease in time.⁸ This change allows for a quicker diagnosis with more flexibility in the imaging criteria.

With regard to spinal cord lesions, panel recommendations specified that a “typical” lesion of MS in the spinal cord would involve little or no swelling of the cord, be at least 3 mm in size, but less than 2 vertebral segments in length, and occupy only part of the spinal cord in cross section. With regard to dissemination in space, a lesion as described above may substitute for an infratentorial lesion, but not for a juxtacortical or periventricular lesion (unlike in the original McDonald criteria, in which a spinal lesion could substitute for any of the 3 aforementioned types of brain lesions). An enhancing spinal cord lesion may be used to fulfill the criteria of an enhancing lesion and an infratentorial lesion at the same time.⁸ Repeat spinal cord imaging was not recommended to establish dissemination of lesions in time for patients who were asymptomatic for myelitis.

The diagnosis of PPMS was simplified in the 2005 revision. Disease progression for 1 year is required, in addition to 2 of the following 3 criteria⁸:

1. Positive brain MRI—9 T2 lesions or 4 or more T2 lesions with positive VEP
2. Two focal T2 spinal cord lesions
3. Positive CSF—oligoclonal IgG bands or increased IgG index, or both

Thus, CSF findings may not be absolutely required for the diagnosis of PPMS.

DIFFERENTIAL DIAGNOSIS OF MS

Clinical manifestations of MS can affect any part of the central nervous system (CNS) and, therefore, may mimic several medical conditions. The use of MRI at the time of clinical presentation can help to reveal the presence or absence of concurrent subclinical demyelinating lesions within the CNS. Such a finding quickly helps to rule out non-demyelinating diseases, such as complicated migraines, intracranial or intraspinal tumors, or other compressive spinal cord lesions, stroke, neurodegenerative condition, such as Parkinson's disease, amyotrophic lateral sclerosis, or Huntington's disease, as well as many other conditions.

Tissue damage and loss may be identified on MRI through the observation of lesions on T1-weighted images with contrast enhancement using Gd, T2-weighted images, T1 hypointensities (also referred to as “black holes”), fluid-attenuated inversion recovery (FLAIR) imaging, and proton density (PD) imaging.⁸ Although MRI scans have improved our objective assessment of MS-related changes in the brain, the relationship between MRI lesion burden using any of these techniques and clinical disease activity remains weak and incomplete.⁹ MRI studies commonly rely on blood-brain barrier leakage (detected using contrast enhancement with Gd on T1-weighted images) as an indicator of acute MS inflammatory activity. This may not be a reliable measure because even chronic MS lesions may be linked to a certain amount of Gd leakage.¹⁰ Although a plaque is likely to demonstrate enhancement in one of its early phases of evolution, the chances of performing the imaging study and missing the roughly 30-day window of inflammatory infiltration are relatively large, and the absence of the Gd enhancement does not signify that the lesion is not still in that early stage. A limitation of T2-weighted images is the inability to distinguish the underlying pathophysiologic heterogeneity of lesions, which may reflect edema, gliosis, remyelination, demyelination, or matrix destruc-

tion.¹¹ T1 hypointensities may not accurately reflect the clinical picture because they are influenced by which particular imaging sequences are used and by variations in technique used by the center to establish the threshold for hypointensity, and are also likely to suffer from intra-individual variations. T1 hypointensities may also be seen in acute stages of inflammation and, therefore, will not predict the conversion of the lesion to a chronic area of tissue destruction. These “black holes” represent only a small portion—perhaps less than 20%—of lesions compared to those seen on T2-weighted imaging.¹² This lack of specificity may introduce yet another degree of uncertainty in the evaluation of serial MRIs in a given patient.

Atrophy and volume changes are considered below. At this time, estimates of volumetric loss of CNS tissue can be performed using freely available software that will run on community MRI machines.

Once the first attack of demyelination has occurred, with its accompanying reversible and irreversible damage to neuronal and other CNS cellular elements within each lesion, certain determinations regarding diagnosis can be made. A recent article by Banwell et al reviewed this process in children, and categorized this first attack based on the localization of symptoms to a single CNS site or multiple CNS sites.¹³ When multiple sites are affected with associated encephalopathy in the patient, a preliminary diagnosis of acute disseminated encephalomyelitis is made. Without encephalopathy, the working diagnosis would be polyfocal demyelination. When symptoms are localized to a single site, the diagnosis was isolated transverse myelitis, isolated optic neuritis, or other. Symptoms localizing to the spinal cord and optic nerve resulted in a diagnosis of neuromyelitis optica. A diagnosis of MS is made only with further demyelinating attacks disseminated in space and time.

MRI IN MS DIAGNOSIS

Over the last decade, there has been a wealth of published data establishing the use of MRI for the diagnosis and management of MS.¹⁴ Additionally, we have seen the benefits of using MRI to measure the effects of disease-modifying therapy in patients with MS.¹⁵ In MS, MRI allows for the measurement of total CNS disease and the detection of subclinical disease, and provides an objective measurement of disease activity with low interobserver variability and greater

sensitivity than the Expanded Disability Status Scale (EDSS).¹⁵

In 2003, the American Academy of Neurology issued a set of recommendations relating to the use of MRI in the diagnosis of MS. According to these guidelines, following the exclusion of alternative diagnoses at baseline, MRI findings were highly accurate in predicting the development of CDMS in patients with CIS. In particular, these recommendations indicated that the presence of 3 or more white matter lesions on a T2-weighted MRI in patients with CIS predicted the development of CDMS within 7 to 10 years with a sensitivity of more than 80%. In addition, the appearance of new T2 or Gd-enhancing lesions following a clinically isolated demyelinating episode provided an accurate predictor of CDMS development in the near term.¹⁶

Also in 2003, in an effort to standardize the use of MRI as a diagnostic tool for MS, a committee of the Consortium of MS Centers established an MRI protocol for MS diagnosis and follow-up. Included in this protocol were guidelines for the use of Gd-enhanced brain MRI in patients with suspected MS. MRI of the spinal cord was suggested if presenting symptoms were at the spinal level or if the brain MRI was non-diagnostic.^{17,18} The committee recommended follow-up evaluation in order to demonstrate new disease activity. In patients with established MS, these recommendations called for a baseline evaluation of the brain with Gd-enhanced MRI, followed by repeat testing upon unexpected clinical worsening for reassessment of disease burden before starting or changing therapy, or to rule out another diagnosis.

These guidelines also recommended standardized MRI protocols based on then-current and widely available technology. Specifically, it was recommended that the MRI field strength be 1 Tesla (T) or greater, slice thickness of the images be less than or equal to 3 mm with no gap, and in-plane resolution of less than or equal to 1 x 1 mm for brain and spinal cord. Recommendations also indicated that scan orientation and coverage must be reproducible, and that the protocol required specific brain sequences, including the sagittal FLAIR, axial PD/T2, axial FLAIR, and Gd-enhanced T1. The recommended spinal cord sequences for this protocol included the sagittal PD/T2, sagittal pre-Gd T1, sagittal post-Gd T1, axial post-Gd T1 through suspicious lesions, and axial T2 through suspicious lesions. The recommended dose of Gd was 0.1 mmol/kg intravenous, with a minimum

delay of 5 minutes before acquiring post-contrast images.¹⁸ Although the use of double- and triple-dose Gd enables the identification of increased numbers of enhancing lesions, the safety and clinical relevance of the information elicited using these doses have not been established.

Although this discussion touches on the importance of CNS evaluation to look for lesion burden and activity, it is well recognized that brain atrophy, which may represent irreversible loss of CNS tissue elements, could play an important role in the management and evaluation of patients with MS.¹⁸ Although earlier measures of brain volume suffered from inconsistent measurement techniques, these have now been circumvented to some degree by the automation of volumetric techniques.¹⁴ Freely available software, which can be used in the imaging protocols of most radiology departments, is primarily used within research centers and has not been incorporated into protocols that radiologists and neurologists are comfortable with. Most evaluators of conventional MRI CNS studies perform rough estimates of overall brain volume losses, thinning of the corpus callosum, brain stem, spinal cord, and so on. Although quantification of such imaging data is clearly a logical next step, it must be recognized that brain atrophy measurement is still limited because of our lack of understanding of the pathophysiologic factors that affect brain volume, and the association between brain volume changes and clinical presentations and outcomes.¹⁹ Another shortcoming of current brain volume measurement is that inflammation with edema and gliosis may, at least temporarily, cause an increase in brain volume, thereby leading to paradoxical increases in volume measurements; such changes may limit the detection of potential tissue losses during this phase of the disease process.¹⁴

A discussion of the use of MRI in MS is not complete without consideration of spinal MRI. There is a well-established correlation between spinal cord atrophy at certain spinal levels and clinical disability.²⁰ It is worth mentioning that this association is validated primarily as a correlate of greater walking disability on the EDSS and has been most useful when incorporated into studies of patients with progressive myelopathic forms of MS.^{21,22} Although measurement of spinal cord atrophy may be useful in clinical practice, it is technically difficult to perform.²³ It is hoped that recent research on these correlations using higher strength magnets, different accessions that can mini-

mize the confounding signal introduced by non-CNS tissue artifact, and improved software capabilities for evaluating and integrating spinal cord injury with the overall CNS radiologic evaluation of MS will improve its usefulness.

It is important to keep in mind that the revised McDonald criteria advise repeating the MRI at 3 months in patients for whom a diagnosis of MS is highly suspicious. Although there is no established standard of care for repeat imaging, current protocols at many MS centers are geared around T1-Gd and FLAIR imaging studies.

ADVANCES IN MRI AND NOVEL IMAGING TECHNIQUES

Cerebral cortical lesions have only recently emerged as a potentially important component in the pathogenesis of MS.^{24,25} Although they have traditionally received relatively little attention, studies indicate that lesions involving cortical gray matter are exceedingly common to the disease.²⁶⁻²⁸ Cortical lesions may occur: (1) at the leukocortical junction, thus demyelinating both white and gray matter; (2) entirely within the cortex; or (3) extending into the cortex from the pial surface.²⁶ One recent study found that cortical demyelination was characteristic of progressive forms of MS.²⁹ It has also been suggested that cortical lesions may help to explain MS-related neurologic symptoms that do not correspond to white matter lesions.²⁴

Unfortunately, current MRI techniques correlate poorly with actual tissue analysis of cortical lesions. In one study, only 3% of postmortem lesions were captured on T2-weighted MRI, and only 5% on FLAIR imaging.³⁰ MRI using Gd-enhanced T1-weighted images only supplies a "snapshot" of clinical information, but fails to detect new plaque activity outside its time of enhancement.¹⁴ Thus, newer "non-conventional" techniques in MRI have been developed to provide more sensitive markers of disease pathology and to better characterize edema, inflammation, demyelination, axonal loss, and neurodegeneration in MS.³¹

One of the newer imaging modalities under development is magnetization transfer ratio (MTR). A reduction in MTR represents a lowered exchange of protons within the tissue upon magnetic imaging and may be associated with demyelination, macrophage infiltration, or axon damage; an increased MTR is associated with remyelination.³² It is thought that changes observed on MTR will predate the onset of

the acute lesion seen by T1-Gd+ imaging, and abnormalities seen using MTR in otherwise normal white and gray matter by conventional acquisitions may provide better imaging correlation with disease activity, response to therapy, and prognosis for clinical progression.³³ MTR may thus be useful in evaluating a patient's response to treatment and clinical course by providing evidence of myelin repair. Potential advantages of MTR include correlation of results with long-term disability and the relative ease with which the test may be conducted.²³ However, validation of its use as a measure of these indices of disease activity has been stymied by difficulties in the standardization of its use across centers in multicenter trials.

High-field-strength MRI scans are more sensitive than the current 1.5T imagers widely used in clinical practice today. High-field scanners using 3T are commonly used at many centers at the present time, and 4+T imaging at magnetic strengths up to 7T and higher in research settings can generate images at higher resolution, resulting in an increase in the number and volume of lesions detected when compared with 1.5T images.³¹ One recent *ex vivo* study found that at 8T, scans detected multiple, discrete cortical lesions, whereas 1.5T images found none.³⁴ As these gains in MRI field-strength make their way out to more common clinical use, magnetic imaging studies will have increased sensitivity in the detection of cortical lesions. As technology advances, the use of such imaging will play a greater role in the diagnosis and management of patients with MS.

Magnetic resonance spectroscopy (MRS) determines the concentration of brain metabolites, including creatine, lactate, N-acetylaspartate (NAA), and choline (Cho), using the signal from hydrogen protons within tissue.³⁵ It is believed that the NAA peak indicates neuroaxonal integrity whereas the Cho peak marks cell membrane metabolism.³⁶ Therefore, a decrease in the NAA peak may represent injury to nerves and axons, and secondarily, irreversible CNS atrophy, whereas a rise in the Cho indicates cell membrane turnover as seen in demyelination, remyelination, gliosis, or inflammation. MRS data can thus provide valuable insights into "the pathogenesis and evolution of disease."³¹ The techniques involved in MRS are burdensome for everyday clinical practice, although MRS has good correlations with clinical disability in relapsing-remitting MS and is useful in research protocols.²³ Better resolution of MRS at high-

er Tesla strengths and the elucidation of tissue changes may also improve MRS relevance to the evaluation of its efficacy as an outcome measure in clinical trials and a measure of CNS health.

By measuring movement of tissue water, diffusion-weighted imaging and diffusion tensor imaging provide information about tissue damage in normal-appearing brain tissue in MS.^{37,38} These data may provide a measure of myelin integrity, but its current use in MS is restricted to research settings.²³

Functional MRI (fMRI) is an indirect measure of blood flow and neuronal activity based on measures of the ratio of oxygenated to deoxygenated hemoglobin in the brain. With increased neuronal activity, minute changes in this ratio can be measured using the blood oxygenation level-dependent imaging technique.³⁹ Although used in research settings to study the neural correlates of neuropsychologic and motor deficits of patients with MS, there are no data on fMRI to suggest correlation with long-term disability, thus hampering the use of this modality in the clinical setting.³¹

Optical coherence tomography (OCT) uses an interferometer to estimate the thickness of the retinal nerve fiber layer (RNFL), using measurements that are based on the echo time-delay of infrared light. This nerve layer consists primarily of unmyelinated axons before they form the optic nerve, thus providing a nearly direct measure of retrograde nerve damage from optic neuritis.⁴⁰ Low-contrast letter acuity and contrast sensitivity are 2 measures of visual function that correlate well with RNFL thickness in patients with MS.⁴¹ RNFL reduction is also seen in the nonaffected eye of patients with MS who have clinically unilateral optic neuritis.⁴² The benefits of OCT include the ease of testing (<5 minutes/eye and may be performed by non-physicians), the low cost compared to MRI evaluation of optic nerve structure, and the ability to correlate directly with visual function.⁴⁰ Despite these benefits, additional research is necessary before OCT can be relied on to measure disability or serve as a marker of disease progression in the face of drug therapy.

CONCLUSIONS

Advances in technology have improved our ability to diagnose and monitor disease progression in patients with MS. Incorporating paraclinical measures of disease, such as MRI, has allowed us to track the course of disease and disability, and to follow the

effects and potential benefits of disease-modifying therapies. Recent advances, such as the implementation of MRS, atrophy measurements, MTR, and OCT, may play a key role in research advances, as well as a future role in the clinical management of patients with MS; however, at this time, they do not qualify as well-characterized surrogate markers of disease activity in a way that would allow us to substitute them for clinical measures of disease activity and progression.

It should be recognized that, although we welcome new ways of monitoring MS to simplify the process, the result, at least in the short term, may be the very opposite. It may be that the information becoming available through these new modalities will raise more questions than answers, create a more complex landscape of disease activity, and make more precise assessments of a therapeutic intervention more problematic, both in individuals and in what we incorrectly consider the homogeneous cohorts studied in clinical trials. At this time, the diagnosis and clinical evaluation of ongoing MS continues to be based on the clinical judgment of the practitioner. To the extent that these new technologies help identify trends and augment that decision-making process, their continued use in skilled hands will improve our confidence in them.

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