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Current and New Directions in MRI in Multiple Sclerosis

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ABSTRACT

Purpose of Review: This article summarizes the use of MRI in the diagnosis and treatment of multiple sclerosis (MS). Current and emerging imaging techniques are reviewed pertaining to their utility in MS.

Recent Findings: Conventional T1-weighted and T2-weighted sequences are used to identify and characterize disease pathology in MS. T2 lesion burden, postcontrast enhancement, T1 hypointensities, and regional and global atrophy are all informative and correlate to clinical measures, such as disease disability, to a variable extent. Newer techniques such as diffusion tensor imaging, magnetization transfer imaging, and MR spectroscopy are increasingly being incorporated into clinical trials and may provide improved specificity to the underlying pathology. Double inversion recovery and ultrahigh-field-strength MRI have direct application in MS for evaluating cortical pathology. Newer functional MRI techniques such as resting-state functional connectivity are increasingly being applied in MS.

Summary: Conventional and emerging imaging techniques greatly inform our understanding of MS. These techniques are integral in diagnosis, in evaluating new treatments for MS, and for following patients in the clinical setting.

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INTRODUCTION

One could argue that neuroimaging has made the single greatest impact on our current understanding of multiple sclerosis (MS) and its treatment. MRI in particular offers an *in vivo* window for examining the underlying pathology of MS. Imaging augments our understanding of the disease by elucidating the mechanism and progression of disability in ways histopathologic studies have never achieved. Today, MRI is commonly used to (1) aid in the diagnosis of MS, (2) help evaluate new MS treatments more efficiently in clinical trials, and (3) follow patients clinically, both on and off disease-modifying therapy. Currently, the primary goals in developing new

imaging techniques in MS include (1) increasing the specificity for the type of underlying pathology, including demyelination and axonal loss; (2) developing improved predictive markers of future disease activity and disability; and (3) developing biomarkers increasingly sensitive to gray matter pathology that was previously underappreciated and understudied.

THE ROLE OF IMAGING IN THE DIAGNOSIS OF MULTIPLE SCLEROSIS

MRI represents perhaps the single most important diagnostic test supporting the diagnosis of MS. Current 2010 McDonald diagnostic criteria for MS (covered in greater detail in the

article “Diagnosis and Differential Diagnosis of Multiple Sclerosis” by Dr Ilana B. Katz Sand and Dr Fred D. Lublin in this issue of **CONTINUUM**) make use of MRI and allow for a diagnosis based on one MRI scan performed at a single point in time by adopting simplified Magnetic Imaging in Multiple Sclerosis (MAGNIMS) criteria for determining dissemination in space (**Case 9-1**).¹ Using these criteria, dissemination in space is established by one or more lesions in at least two of the following four locations: periventricular, juxtacortical, infratentorial, and spinal cord (symptomatic brainstem and spinal cord lesions do not contribute to lesion count). In addition, MRI often effectively excludes other diseases of the CNS. Typical clinical MRI protocols currently include conventional sequences based on T1-weighted and T2-weighted imaging.

T2-Weighted Sequences

White matter lesions characteristic of MS are best seen on fluid-attenuated inversion recovery (FLAIR) sequences that suppress signal from the CSF and allow for increased sensitivity in detecting periventricular hyperintense lesions. The characteristic ovoid-appearing white matter hyperintensities on MRI have a predilection for periventricular and juxtacortical locations (**Figures 9-2A and 9-2B**). In contrast, nonspecific, small, round T2 hyperintensities typical for microvascular disease or migraine headache are observed in a subcortical location (**Figure 9-2C**). The periventricular distribution of MS lesions relates to the association with venules that is obvious on histopathology, ultrahigh-field-strength MRI (**Figure 9-3**), and a newly developed technique at 3 Tesla combining FLAIR and gradient echo T2*-weighted contrasts on a single

image, called FLAIR*.² Of note, the presence of a central vein, as demonstrated at higher field strengths, helps distinguish MS lesions from white matter lesions in other conditions and brain abnormalities seen in neuromyelitis optica (NMO).^{3,4} The corpus callosum is of particular regional interest because of its relative specificity as a common site of MS lesions and potential relationship to cognitive dysfunction.⁵ Visualization of the corpus callosum is optimized by inclusion of a sagittal FLAIR sequence in an MS-protocol MRI (**Figure 9-4**).

Other infratentorial brain locations with a predilection for MS plaques include the cerebellum, cerebellar peduncles, and brainstem. In contrast to the supratentorium, posterior fossa lesions are better visualized with T2-weighted and proton density images compared to FLAIR because of flow-related artifacts and poor lesion contrast (**Figure 9-5**).

Contrast Enhancement and T1-Weighted Sequences

Inflammation in acute demyelinating MS lesions causes increased blood-brain barrier permeability. This leads to contrast enhancement on post-gadolinium T1-weighted imaging. Contrast enhancement typically persists for 1 month on average, allowing for the dichotomization of MS lesions into acute and chronic lesions.⁶ Contrast enhancement is less commonly seen in progressive phases of MS. However, its presence in progressive MS may predict response to disease-modifying treatments that target inflammation.⁷

Enhancement patterns are variable but can be classified as nodular, punctate, or ringlike (**Figure 9-6**). Some lesions, particularly those with a tumefactive (ie, tumorlike) appearance, show an open-ring pattern,⁸ which may be helpful in discriminating

KEY POINTS

- The 2010 revised McDonald criteria adopt simplified Magnetic Imaging in Multiple Sclerosis (MAGNIMS) criteria for determining dissemination in space.
- Dissemination in space is established by one or more lesions in at least two of the following four locations: periventricular, juxtacortical, infratentorial, and spinal cord (symptomatic brainstem and spinal cord lesions do not contribute to lesion count).
- The periventricular distribution of multiple sclerosis lesions relates to the association with venules.
- The corpus callosum is a common site of multiple sclerosis lesions and is optimally viewed on sagittal fluid-attenuated inversion recovery (FLAIR) images.
- Contrast enhancement is less commonly seen in progressive phases of multiple sclerosis.

Case 9-1

A 28-year-old woman who was 4 months postpartum developed vertigo and diplopia that gradually improved over 4 days and eventually resolved. She had no history of other neurologic symptoms. Her neurologic examination was normal. Brain and spinal cord MRI showed multiple foci of T2 hyperintensity in the periventricular and juxtacortical white matter, cerebellum, brainstem, genu of the corpus callosum, and cervical spinal cord, including two contrast enhancing lesions (**Figure 9-1**). The patient was diagnosed with multiple sclerosis (MS) and started disease-modifying therapy. A repeat brain MRI performed 6 months after treatment initiation was unchanged and without evidence of contrast enhancing lesions.

Comment. This case represents a typical presentation for MS. The presence of T2-hyperintense lesions in locations typical for MS satisfies 2010 McDonald criteria for dissemination in space, and the presence of enhancing and nonenhancing lesions satisfies criteria for dissemination in time based on the initial MRI. As is common in clinical practice, a repeat MRI 6 months after starting therapy assesses for the presence of breakthrough disease. If evidence of disease activity is present, even if asymptomatic, consideration should be given to alternative therapies for patients with suboptimal treatment response on MRI.

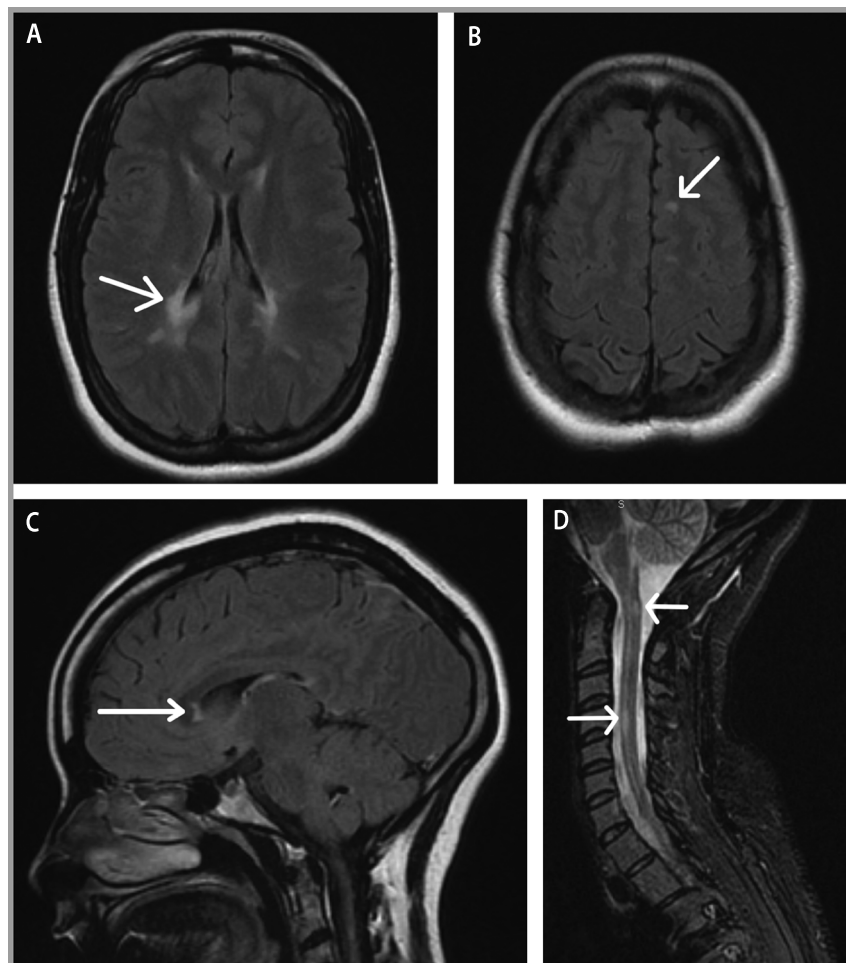


FIGURE 9-1 Brain and spinal cord MRI. Brain MRI at the time of diagnosis demonstrates *A*, periventricular lesions (*arrow*); *B*, juxtacortical lesions (*arrow*); and *C*, corpus callosum lesions (*arrow*) on fluid-attenuated inversion recovery (FLAIR) sequences. *D*, Spinal cord short T1 inversion recovery (STIR) image reveals lesions at C1 and C4 (*arrows*).

a demyelinating lesion from abscess or neoplasm. Recognition of tumefactive MS on the differential diagnosis of ring enhancing and open-ring enhancing

lesions may preclude the need for tissue biopsy where the underlying diagnosis is unclear. The enhancement pattern can evolve over time,

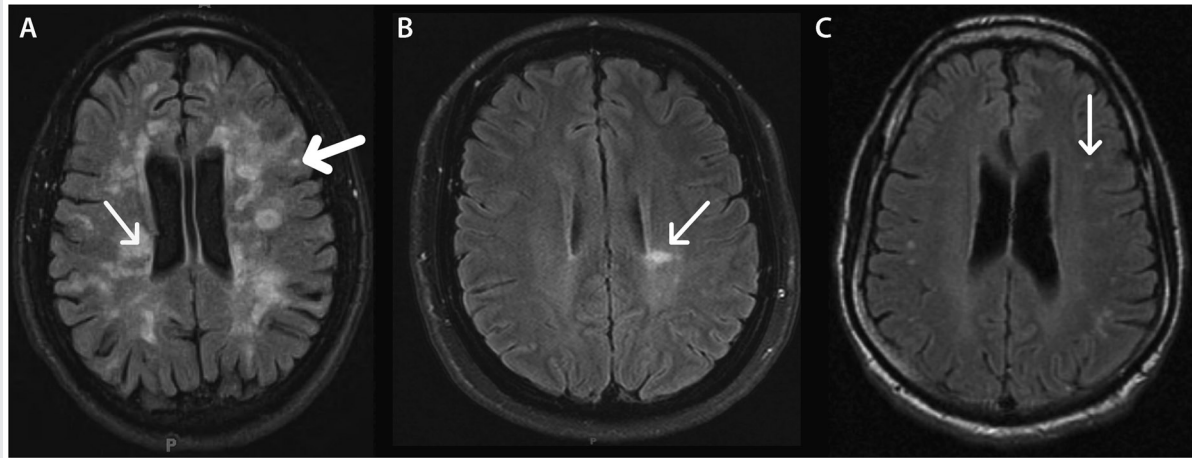


FIGURE 9-2 Location and appearance of multiple sclerosis (MS) lesions on fluid-attenuated inversion recovery (FLAIR) images. In MS, hyperintense FLAIR lesions are typically seen in periventricular (*thin arrow*) and juxtacortical (*thick arrow*) locations (A). Some lesions can radiate perpendicularly away from the lateral ventricles as fingerlike projections (*arrow*), termed “Dawson fingers” (B). In other diseases such as migraine, T2 hyperintensities tend to be small and round in appearance and subcortical in location (*arrow*) (C), although these lesions can also be seen in MS.

with nodular lesions enhancing centrifugally (ie, outward) and ringlike enhancing lesions enhancing centripetally (ie, inward).⁹ There is value in having postcontrast T1 sequences in the axial, coronal, and sagittal planes incorporated into a clinical MS-protocol MRI to better increase the sensitivity of detecting contrast enhancing lesions.

Delaying imaging after contrast administration will also increase sensitivity.

In addition, T1 hypointensities (also termed “black holes”) are characteristic of some but not all lesions at the time of contrast enhancement (Figure 9-7). A minority of acute T1 hypointensities will be persistent (lasting longer than 12 months), while

KEY POINT

- Recognition of tumefactive multiple sclerosis on the differential diagnosis of ring enhancing and open-ring enhancing lesions may preclude the need for tissue biopsy where the underlying diagnosis is unclear.

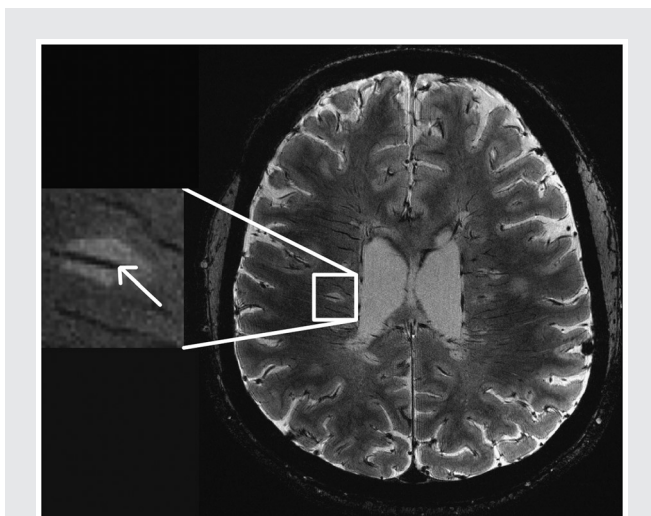


FIGURE 9-3 This fast low-angle shot (FLASH) T2*-weighted image at 7 Tesla demonstrates multiple lesions with venules coursing through (*arrow*).

KEY POINT

■ Persistent T1 hypointensities are correlated with greater tissue damage and increased axonal damage on histopathology.

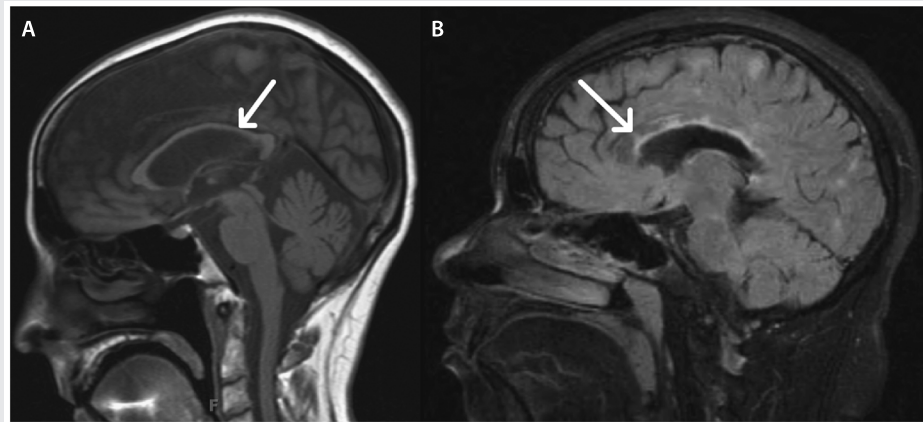


FIGURE 9-4 Corpus callosum imaging. *A*, A sagittal T1-weighted image shows significant corpus callosal thinning (*arrow*), indicative of atrophy. *B*, In a different patient, focal lesions (*arrow*) within the corpus callosum are visualized.

others resolve and become isointense (termed “transient black holes”). Characteristics that predict persistence of black holes include a ring enhancing pattern of gadolinium enhancement, enhancement on two or more monthly MRIs, and enhancement greater than 6 mm in diameter.¹⁰ Chronic T1 hypointensities are correlated with greater tissue damage and increased axonal damage on histopathology.¹¹

Brain Atrophy

Atrophy progresses in MS at a rate (0.5% to 1% per year) greater than that observed in typical aging (see **Figure 9-7**). Considered a substrate for clinical disability and cognitive dysfunction, atrophy can occur early in the disease course of MS.¹² Atrophy can be characterized as a global phenomenon in MS, occurring in both white matter and gray matter, but can

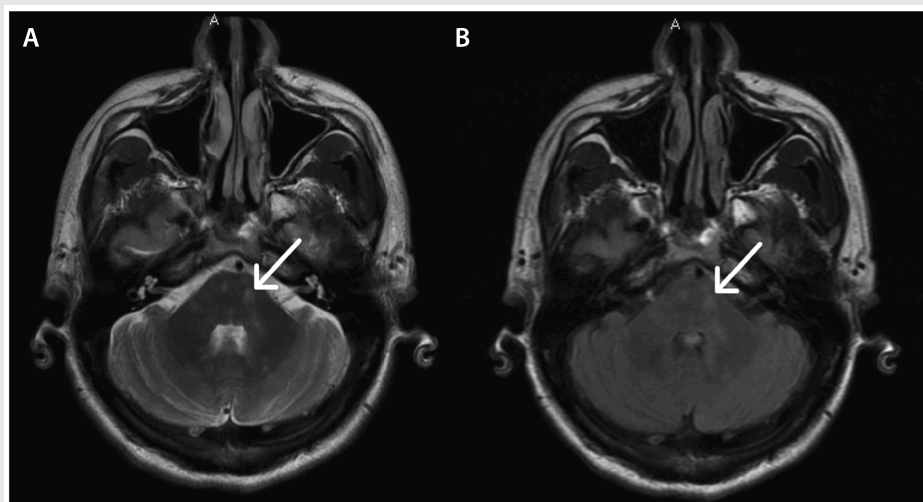


FIGURE 9-5 Demyelinating lesions in the posterior fossa (*arrows*) are typically visualized better with T2-weighted images (*A*) as compared to fluid-attenuated inversion recovery (FLAIR) images (*B*).

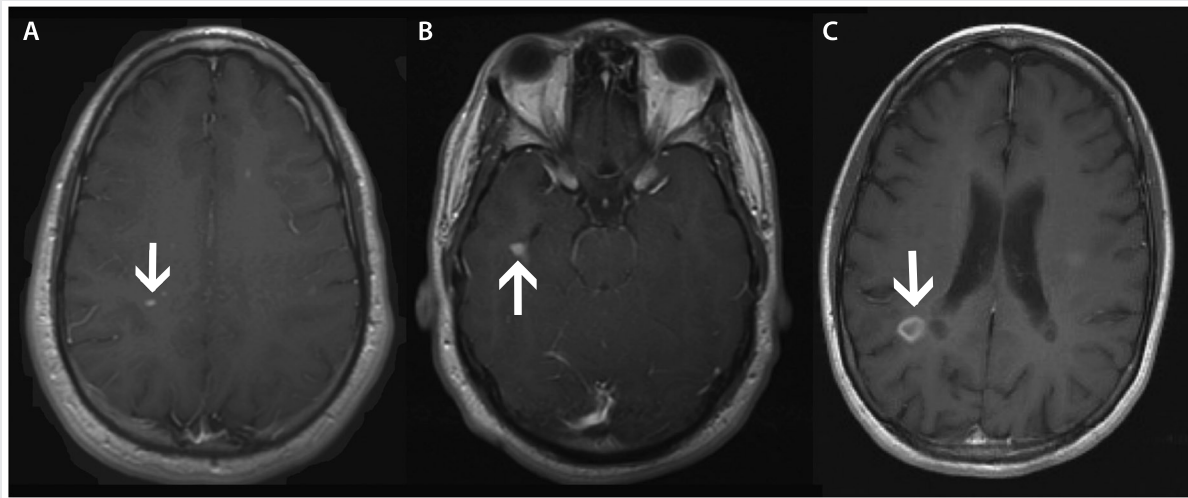


FIGURE 9-6 Patterns of contrast enhancement on postcontrast T1-weighted images include punctate (*arrow*) (A), nodular (*arrow*) (B), and ringlike (*arrow*) (C).

also be evaluated on a regional basis. More advanced computational methods allow for brain segmentation into gray and white matter.¹³ Furthermore, deep gray matter can be excluded to produce a cortical atrophy

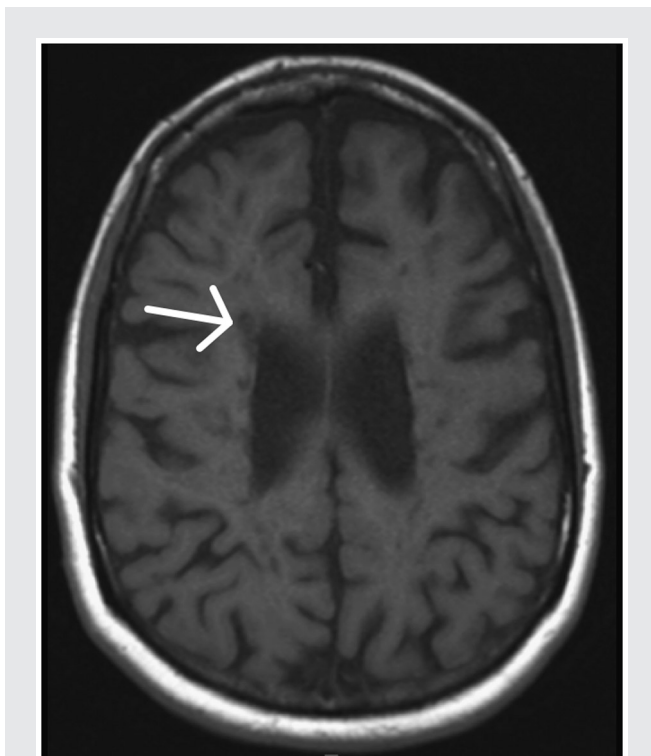


FIGURE 9-7 T1-weighted imaging in a patient with MS exhibits significant atrophy with prominent sulci and numerous T1 hypointensities (*arrow*).

KEY POINTS

- Gray matter atrophy may correlate with physical disability to a greater extent than white matter atrophy.
- Atrophy starts early in the disease and continues into progressive stages.



FIGURE 9-8 Spinal cord short T1 inversion recovery (STIR) images in the sagittal (A) and axial (B) planes demonstrate eccentric lesions (arrows) that span less than one vertebral segment in a patient with multiple sclerosis.

measure. A preponderance of evidence suggests that segmented gray matter atrophy correlates better with clinical disability than white matter atrophy, although with some conflicting re-

sults.^{14,15} The mechanism of gray matter atrophy and its relationship to white matter disease remains an area of intense interest. Atrophy continues in the progressive phases of MS when the inflammatory component of the disease has diminished, providing an imaging outcome of particular interest in clinical trials evaluating potential neuroprotective agents geared toward progressive MS.¹⁶

Of the regional white matter structures, corpus callosum atrophy is widely appreciated in MS and correlates with level of disability (see **Figure 9-4**).¹⁷ The thalamus represents a deep gray matter structure with a relationship to cognitive dysfunction.¹⁸ Thalamic atrophy predicts conversion of clinically isolated syndrome (CIS) to MS and progression of disability.^{19,20} Regional hippocampal atrophy in the cornu ammonis (CA) 1 region is reported in relapsing-remitting MS and associated with memory-encoding dysfunction.²¹

Spinal Cord Imaging

Spinal cord imaging provides additional support for the diagnosis of MS in many instances. Spinal cord abnormalities are described in more than 80% of patients recently diagnosed with MS, with a proclivity for the cervical cord.²² Spinal cord lesions tend to span one vertebral segment or less. They tend to be located in an eccentric, dorsal, or lateral location in the axial plane of the cord and span less than half of the axial cord (**Figure 9-8**). In contrast, NMO spinal cord lesions are more likely to be longitudinally extensive, affect the spinal cord gray matter, and have associated T1 hypointensity.²³

USING NEUROIMAGING TO MONITOR PATIENTS WITH MULTIPLE SCLEROSIS

Subclinical inflammatory disease activity occurs commonly in MS and is

Case 9-2

A 55-year-old woman experienced an episode of difficulty reading the newspaper. Approximately 30 minutes later, she had trouble expressing herself when ordering coffee, lasting only seconds. Workup for these symptoms included imaging studies to evaluate for ischemia. Brain MRI was potentially consistent with demyelination with 10 T2 hyperintensities, some with the appearance of Dawson fingers (Figure 9-9A). Spinal cord imaging was normal (Figure 9-9B). Family history was notable for multiple sclerosis (MS) in her sister. Without clinical events definitely attributable to demyelinating disease, the patient was diagnosed with a radiologically isolated syndrome. She did not start treatment for MS at that time. Serial imaging remained unchanged until 1 year later in the setting of left arm numbness. At that time, new cervical spinal T2 hyperintensities were discovered, including one at C1-2 (Figure 9-9C).

Comment. This case highlights the importance of closely following patients (clinically and with MRI) who are at a particularly high risk of converting to MS and are not currently on disease-modifying therapy. In this case, it was helpful to have baseline spinal cord imaging (which was normal) to clearly demonstrate progression of disease that corresponded with subsequent symptoms.

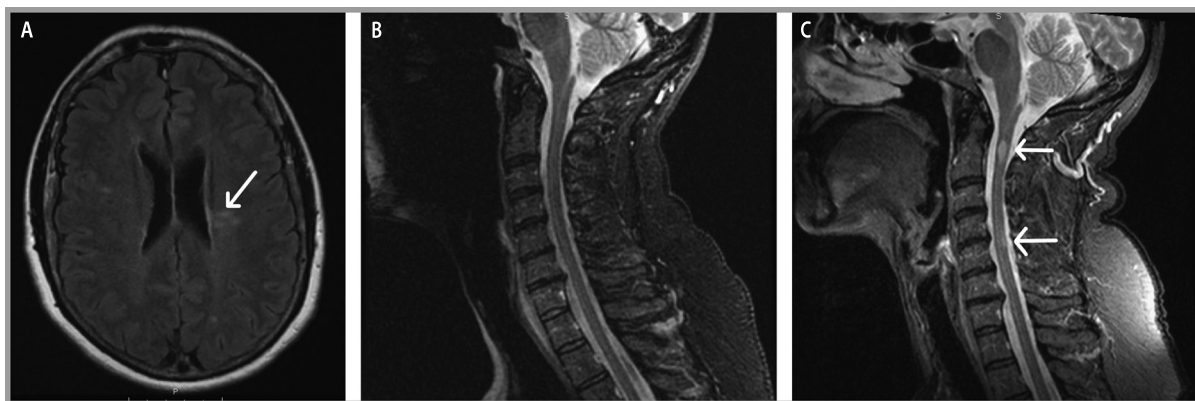


FIGURE 9-9 Baseline and follow-up brain MRI. *A*, Brain MRI is remarkable for characteristic Dawson fingers (arrow). *B*, Initial spinal cord MRI was normal. *C*, Follow-up spinal cord imaging 1 year later shows interval development of lesions at C1-2 and C4-5 (arrows).

captured to some extent by conventional MRI. Serial MRI can be employed in a number of clinical scenarios. Some patients with a first clinical demyelinating event (ie, CIS) will initially defer starting long-term MS disease-modifying therapy. In these cases, MRI helps monitor for asymptomatic inflammatory disease activity that may tip the balance for making the decision to start disease-modifying therapy. Radiologically isolated syndrome, in which an abnormal brain MRI consistent with MS is incidentally discovered, represents another group

at high risk of developing clinically definite MS. **Case 9-2** highlights the importance of closely following patients (clinically and with MRI) who are at a particularly high risk of converting to MS.

For patients who are treated with a disease-modifying agent for MS, MRI is commonly used to assess the efficacy of the selected therapy. A follow-up MRI should be performed 6 to 12 months after starting a new therapy. In a large retrospective study of MS patients on therapy, the presence of more than two enhancing lesions at 1

KEY POINT

- Subclinical inflammatory disease activity occurs commonly in multiple sclerosis and is captured to some extent by conventional MRI.

year was a predictor of poor clinical outcomes at 5 years.²⁴ Annual to biannual monitoring of brain imaging during the relapsing stage of MS is commonly practiced despite the lack of clear consensus. While monitoring with MRI offers only a snapshot of contrast enhancing lesions, new or enlarging T2 lesions and new T1 hypointensities may also be monitored. Brain imaging is generally considered a more sensitive surveillance

tool than spinal cord imaging for longitudinal monitoring. In addition, brain imaging is more likely to identify subclinical inflammation, where inflammation affecting the spinal cord is more likely to be symptomatic. Considerations for time and cost constraints may limit spinal cord MRI for monitoring MS treatments.

Currently, a notable drawback of monitoring patients with serial imaging is the inability to follow changes in

Case 9-3

A previously healthy 27-year-old man presented with bilateral hand numbness. In retrospect, he reported experiencing 1 month of groin numbness 4 years ago. He denied a history of vision changes or other neurologic symptoms. Neurologic examination was remarkable only for lower extremity hyperreflexia and bilateral ankle clonus.

Spinal cord imaging revealed multiple T2 hyperintensities intrinsic to the cord, with an enhancing lesion at C2. Brain MRI supported the diagnosis of multiple sclerosis with innumerable T2 hyperintensities in a periventricular and juxtacortical distribution and a severe disease burden (Figure 9-10). A minority of the lesions exhibited T1 hypointensity. A total of seven gadolinium-enhancing lesions were present.

Comment. This case illustrates the discrepancy that is not uncommon between T2 lesion load and physical disability. In this case, few T1 hypointensities were evident, perhaps leading to the paucity of symptoms and examination findings. In light of the many enhancing lesions, one might consider treating this patient more aggressively to control the active inflammatory component of his disease and to preserve the low level of disability.

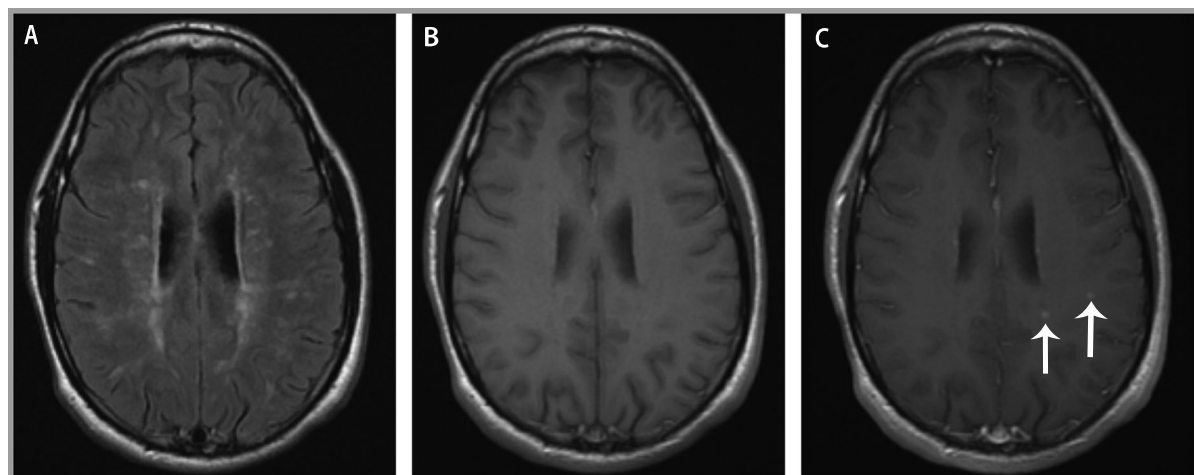


FIGURE 9-10 Brain MRI. A, Brain MRI shows multiple lesions on fluid-attenuated inversion recovery (FLAIR) but, B, few T1 hypointensities. C, Postcontrast T1-weighted images show several enhancing lesions (arrows) on this slice.

brain atrophy in clinical practice. In addition, an unchanged brain MRI based on conventional sequences may give a false sense of security of disease stability, when in fact conventional sequences may be relatively insensitive to subtle changes. These issues necessitate development of more advanced techniques that can quantify changes in normal-appearing white and gray matter. Once these advanced techniques are fully validated and automated for quantitation, the goal is to incorporate them into the care of individual patients.

ADVANCED IMAGING METHODS FOR IMPROVING SPECIFICITY FOR UNDERLYING PATHOLOGY

Conventional MRI sequences lack a true specificity for underlying pathology of a given lesion. Hyperintense T2 lesions can contain a variable extent of demyelination, remyelination, axonal loss, inflammation, and edema. This variability may explain some of the discrepancy that can be seen between T2 lesion load and clinical disability, as exemplified by **Case 9-3**. Application of advanced quantitative imaging tech-

niques addresses these deficiencies by attempting to improve the specificity for detecting the extent of demyelination or axonal loss. Diffusion tensor imaging (DTI), magnetization transfer imaging, and proton magnetic resonance spectroscopy have each been studied extensively and are being incorporated as secondary outcome measures in many clinical trials. Ultrahigh-field MRI and functional MRI (fMRI) provide additional means to understand disease mechanism and progression.

Diffusion Tensor Imaging

DTI may serve to evaluate the structural integrity of white matter and can also be used for probabilistic or deterministic tractography (**Figure 9-11**). Both methods make use of the directional diffusion of water in tissue, which is affected by surrounding structures in CNS white matter. In normal white matter, water diffusion is greater in the direction parallel to axons (ie, axial diffusivity [AD]) than perpendicular to axons (radial diffusivity [RD]). Mean diffusivity (MD) and fractional anisotropy (FA) are other descriptive

KEY POINT

- Advanced techniques that can increase the specificity for the underlying pathology in multiple sclerosis may improve evaluation of new treatments for the disease, including progressive multiple sclerosis.

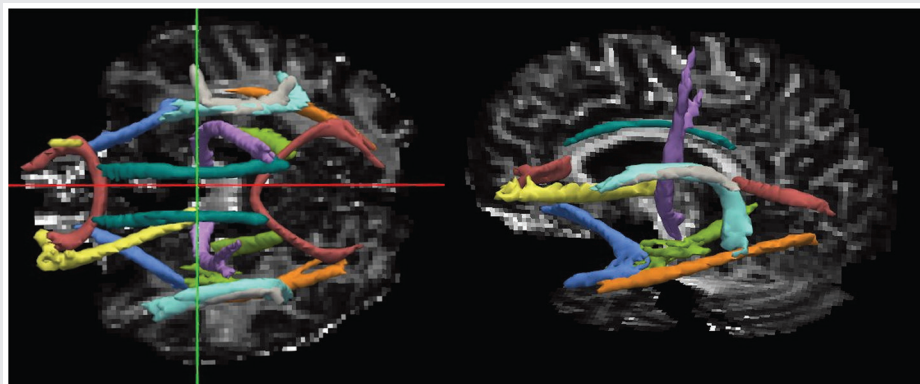


FIGURE 9-11 A probabilistic global tractography tool called Tracts Constrained by Underlying Anatomy (TRACULA) is used to reconstruct the major white matter tracts using diffusion tensor imaging (DTI) and anatomical constraints in a patient with multiple sclerosis. Diffusion tensor imaging parameters can be derived from any of the reconstructed white matter tracts. This method precludes the need to manually draw regions of interest to derive DTI measures.

KEY POINT

■ Diffusion tensor imaging, magnetization transfer ratio, and magnetic resonance spectroscopy are all capable of detecting changes throughout the brain of multiple sclerosis patients, including normal-appearing white matter.

summary parameters derived from the diffusion characteristics. In animal models, increased RD correlates greatest with demyelination, and decreased AD correlates with acute axonal damage.²⁵ In some in vivo studies of MS, RD appears to provide the closest correlation with tissue integrity.²⁶ The association of AD and axonal damage in MS is less well established. DTI provides evidence for the revelation that white matter that appears normal on conventional imaging techniques, so-called normal-appearing white matter, is in fact not normal. Microglial activation and axonal pathology may explain this phenomenon.²⁷ A multicenter validation study indicated that FA is the most comparable DTI measure across centers and supports its use in multicenter clinical trials.²⁸

Magnetization Transfer Imaging

Magnetization transfer imaging is based on the transfer of magnetization between semisolid and water protons in different structural environments. In intact white matter myelin, protons are bound to macromolecules such as lipids, yielding a high magnetization transfer ratio (MTR). In contrast, in areas of demyelination, decreased binding of protons reduces MTR.²⁹ Longitudinal studies demonstrate decreases in MTR preceding contrast enhancement. There is marked reduction in MTR during contrast enhancement, followed by partial or complete resolution as inflammation reduces and remyelination occurs.³⁰ Because of these features, this technique provides a promising primary outcome measure to evaluate remyelinating therapies in clinical trials. Several metrics that have been proposed for further study include intralésional MTR and whole-brain MTR.³¹ MTR may also provide insight into gray matter pathol-

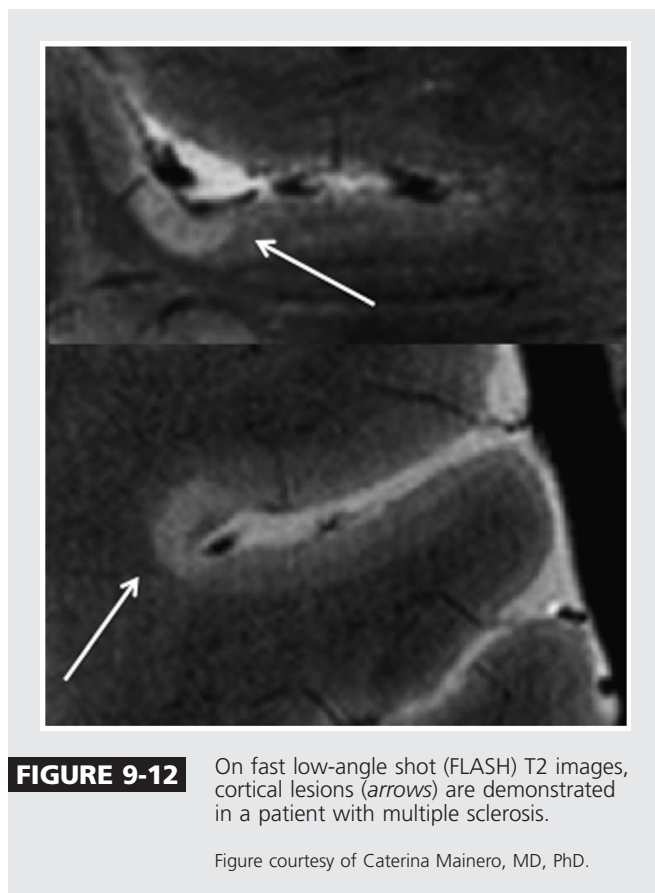
ogy, which is not well visualized using conventional imaging.³²

Proton Magnetic Resonance Spectroscopy

Proton magnetic resonance spectroscopy detects metabolites in the neural tissues. *N*-acetylaspartate (NAA) is found in neurons and their processes and represents a candidate marker for axonal loss. A longitudinal study demonstrates a decrease in whole-brain NAA over a 2-year period in relapsing-remitting MS.³³ Another study evaluated the ratio of *myo*-inositol, a marker of astrogliosis, to NAA in MS. The ratio of *myo*-inositol to NAA predicted future atrophy and disability progression.³⁴ A new method of applying the technique of DTI to spectroscopy is termed “diffusion tensor spectroscopy.” Preliminary results indicate that reduced diffusion of NAA along axons may represent a marker of axonal damage.³⁵

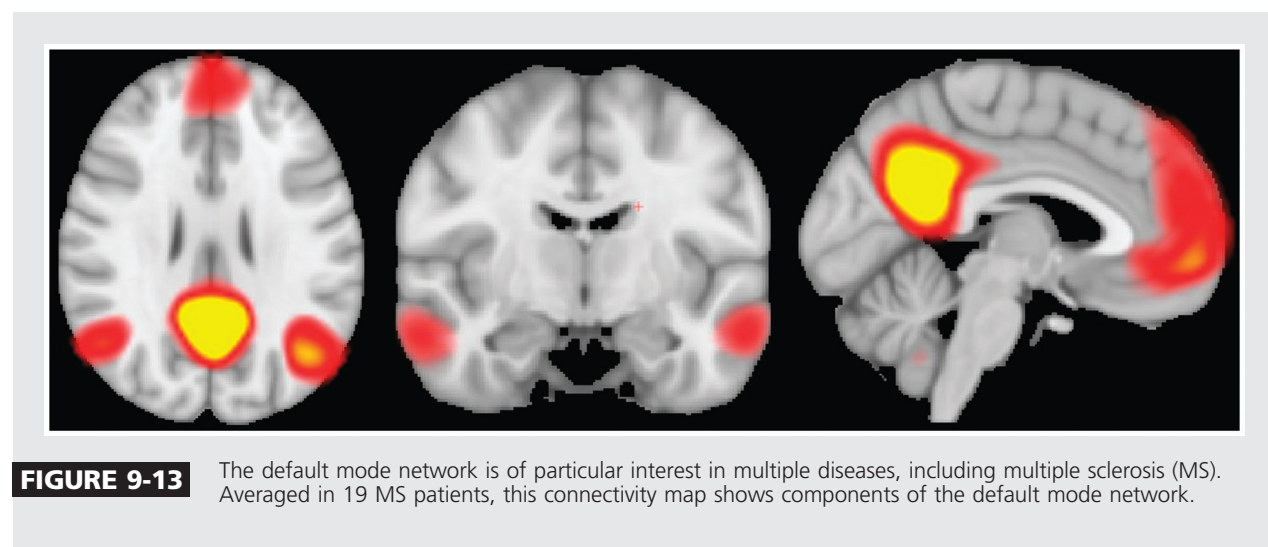
Advanced Spinal Cord Imaging

Applying the above-mentioned advanced imaging techniques in the spinal cord can be technically challenging for various reasons, including physiologic motion (ie, respiration, cardiac pulsation, CSF pulsation) and magnetic field inhomogeneity due to nearby vertebrae. However, various advanced imaging sequences have potential to better quantify the contribution of spinal cord pathology to level of disability. Atrophy also occurs in the spinal cord in MS and correlates to a greater extent with disability than other brain measures of atrophy in patients with mild disability.³⁶ Spinal cord atrophy holds attraction as an outcome measure in progressive MS clinical trials because of the close relationship of this stage of MS with spinal cord damage. Other advanced techniques, such as DTI and MTR, can



be implemented in the spinal cord but require careful attention from an MR physicist to reduce artifacts. These techniques allow for tract-specific measurements by placing regions of interest in the dorsal column or lateral

corticospinal tracts of the spinal cord. Using these tract-specific techniques, differences between MS and NMO (a disease known to have greater tissue destruction) can be observed.³⁷ In a separate large study examining



KEY POINT

■ Double inversion recovery and ultrahigh-field 7-Tesla MRI detect cortical lesions, although each technique has its own limitations.

quantitative spinal cord measures such as spinal cord atrophy, DTI, and MTR, independent association of FA, MD, RD, and MTR with level of disability was observed.³⁸ As the application of these techniques to the spinal cord continues to progress, it may eventually be possible to better incorporate spinal cord imaging into therapeutic clinical trials.

Imaging Cortical Pathology

Focal cortical demyelination has been long observed in autopsy studies of MS.³⁹ However, identification of cortical lesions in vivo eludes clinicians at traditional field strengths. Several techniques have been championed to evaluate cortical pathology in MS. One attractive 3-Tesla technique is double inversion recovery (DIR), often used in conjunction with phase-sensitive inversion recovery (PSIR). Two inversion pulses suppress signal of both CSF and white matter in DIR. Intracortical lesions detected by DIR and PSIR are associated with cognitive dysfunction in MS.⁴⁰ Because DIR can be implemented on 3-Tesla platforms, it offers the advantage of universal incorporation into clinical trials and clinical practice. However, DIR imaging suffers from signal artifacts that can be confused with cortical lesions and may lead to poor interrater reproducibility in identification of cortical lesions, even after implementing consensus recommendations.⁴¹ In addition, compared to higher field strengths, DIR suffers lower sensitivity for detecting cortical lesions, particularly subpial lesions.⁴²

Compared to conventional field strengths, ultrahigh-field 7-Tesla MRI takes advantage of significant increases in signal-to-noise ratio to increase spatial resolution. The increased resolution notably decreases the partial volume effect between the gray matter

and adjacent CSF and white matter. Ultrahigh-field imaging has allowed improved sensitivity for detecting cortical lesions of all subtypes (leuko-cortical spanning white and gray matter, intracortical, and subpial) that closely mirror subtype distribution described in ex vivo studies (**Figure 9-12**).⁴³ In addition, an overall subpial signal increase in specific areas of the cortex in MS patients compared to healthy controls provides evidence for the in vivo existence of disseminated subpial changes in MS.⁴⁴ Pathologic correlation studies indicate that ultrahigh-field imaging has reasonable sensitivity for detecting cortical lesions.⁴⁵ Once cortical lesions can be reliably detected on universal platforms, they can be incorporated into diagnostic criteria, likely increasing both the sensitivity and specificity of criteria.

Functional MRI

Functional MRI offers the advantage over other discussed imaging techniques by providing evidence for plasticity in MS. A recent application of fMRI is the discovery of a highly and specifically organized spontaneous component of blood oxygen level-dependent (BOLD) signal that is present while the brain is at rest.⁴⁶ The correlation of regions of spontaneous resting-state BOLD fluctuations has been termed “functional connectivity.” These low-frequency (less than 0.1 Hz) fluctuations in BOLD occurring in synchrony in multiple regions are believed to reflect monosynaptic or polysynaptic anatomical connections and distributed neuronal networks (**Figure 9-13**). Several studies have demonstrated decreased functional connectivity in transcallosal sensorimotor pathways in MS compared to control subjects.⁴⁷ Evidence shows increased connectivity in networks of patients with a CIS.⁴⁸ Conversely,

decreased functional connectivity in the default mode network (cortical areas activated while the brain is engaged in inward tasks) is seen in progressive MS compared to control subjects.⁴⁹ These results suggest an early adaptive mechanism in MS patients that is eventually overcome following increased disease burden. Resting-state functional connectivity may have future applications to elucidate the cause of cognitive dysfunction in MS.

CONCLUSION

MRI is integral to making the early and accurate diagnosis of MS. It provides valuable information for monitoring patients to identify the level of treatment response. The goal of emerging techniques is to provide markers more sensitive to changes in the disease and more specific to the underlying pathology. In doing so, improved correlation with current and future levels of disability can be achieved.

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KEY POINT

- Functional MRI may have application for observing and quantifying adaptive plasticity in multiple sclerosis.

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