MRI in Diagnosis and Disease Monitoring

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Introduction

The introduction of magnetic resonance imaging (MRI) in multiple sclerosis (MS) has revolutionized our ability to diagnose the disease and monitor treatment response in the clinic and in clinical trials. It has, no less, deepened and transformed our understanding of the pathologic processes involved in the development and progression of the disease. On average, MRI is about 5–10 times more sensitive to ongoing inflammatory demyelination than clinical assessment (Harris *et al*. 1991) and is greatly superior to any other imaging method for lesion detection. McDonald and colleagues introduced MRI into the diagnostic criteria, emphasizing the presence of brain and spinal cord lesions and enabling earlier, more sensitive, and more specific diagnosis than considering clinical symptoms and signs alone. These MRI-based diagnostic criteria have twice been revised since they were first established in 2001, most recently in 2010 (Polman *et al*. 2011) (Table 4.1).

MRI has also provided new insights into the pathogenesis of the disease, particularly with respect to the blood–brain barrier. In this regard, the key observation was that MRI performed after intravenous injection of chelates of gadolinium can detect blood–brain barrier opening occurring during lesion development (Grossman *et al*. 1986). MRI scanning also enabled the noninvasive and quantitative characterization of brain atrophy in MS, which occurs two to three times more rapidly than in the general population and which is generally thought to reflect the neurodegeneration that underlies the relentless accumulation of disability in progressive MS (De Stefano *et al*. 2010). MRI measurements such as T2 and T1 lesion volume, as well as the number of enhancing lesions, have also improved monitoring of the anti-inflammatory effects of disease-modifying therapies in clinical trials (Petkau *et al*. 2008).

This chapter has three main parts. First, we present the MRI findings that are useful to note on initial examination of a patient being worked up for MS. Second, we describe the use of MRI to monitor disease evolution over time, emphasizing insights from clinical trials that can be used in the clinic. Finally, we briefly present some of the most promising advanced MRI techniques.

Table 4.1 2010 MRI Criteria for Multiple Sclerosis

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks*; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[†]	None[*]
≥2 attacks*; 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)[§]; or Await a further clinical attack* implicating a different CNS site
1 attack*; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan or Await a second clinical attack*
1 attack*; objective clinical evidence of 1 lesion (clinically isolated syndrome)	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)[§]; or Await a second clinical attack* implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack*

| Insidious neurological progression suggestive of MS (PPMS) | 1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[§]: 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 oligoclonal bands 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."

CNS, central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; IgG, immunoglobulin G; MRI, magnetic resonance imaging; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis.

*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 h, 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 h. Before a definite diagnosis of MS can be made, at least one attack must be corroborated by findings on neurological examination, visual evoked potential 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.

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

[‡]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.

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

- *Conventional MRI*
  - The longitudinal (T1) and transverse (T2) relaxation of protons, when placed inside a strong magnetic field and irradiated with radiofrequency energy, can be used to generate images.
  - T2-FLAIR images are the standard for diagnosing MS. They differ from standard T2 images in that signal from free water, mostly cerebrospinal fluid, is suppressed by means of an *inversion pulse*.
  - STIR is another type of T2 image that is especially useful in evaluating the spinal cord and optic nerve.
  - Proton density images are useful for evaluating the brainstem and cerebellum, but newer T2-FLAIR protocols that acquire high-resolution data simultaneously from the whole brain (rather than slice by slice) may be equally good.
  - Intravenous gadolinium shortens T1 relaxation in blood vessels and areas of blood–brain barrier opening. This causes brightening (enhancement) in T1 images.
- *Nonconventional MRI*
  - Magnetization transfer images are indirectly sensitive to macromolecules, which in white matter are mostly contained in myelin.
  - Diffusion images measure the mobility of water molecules and provide indirect information about tissue orientation and microstructure.
  - In spectroscopy, the signal derives from brain metabolites including creatine, *N*-acetylaspartate (NAA) (found almost exclusively in neurons), choline, glutamate, lactate, and myoinositol.
  - Susceptibility (T2*) images are sensitive to small variations in the magnetic field induced by metals such as iron or gadolinium, certain types of tissue (notably myelin), and tissue orientation.

MRI at presentation

Lesions

On a gross anatomic level, MRI correlates well with pathology. Lesions visualized on MRI are usually small, round or oval in shape, asymmetrically distributed across the brain and spinal cord, and seen most readily in the white matter (Figure 4.1). Lesions are typically discrete at first and become more confluent as they accumulate. New lesions are usually clinically silent unless they substantially disrupt a clinically eloquent pathway, which happens most commonly in the optic nerve, brainstem, or spinal cord. However, even lesions in those locations can appear without accompanying symptoms. For differentiation of lesions due to MS from those due to other conditions, important features of lesions include morphology, signal intensity, location, and the presence and character of enhancement following gadolinium administration.

Signal intensity and morphology

Lesions in the acute phase are typically brighter than surrounding white matter (hyperintense) in proton density and T2 images, which most likely reflects a combination of inflammation, demyelination, and increased water content (edema), and they may have fuzzy borders. These same pathological characteristics, but particularly increased water content, cause acute lesions to be darker than surrounding white matter (hypointense) in T1 images. Enhancement (hyperintensity in T1 images) is due to opening of the blood–brain barrier. Older lesions are usually more sharply demarcated, persistently hyperintense in proton density and T2 images and isointense or hypointense in T1 images, and do not enhance with
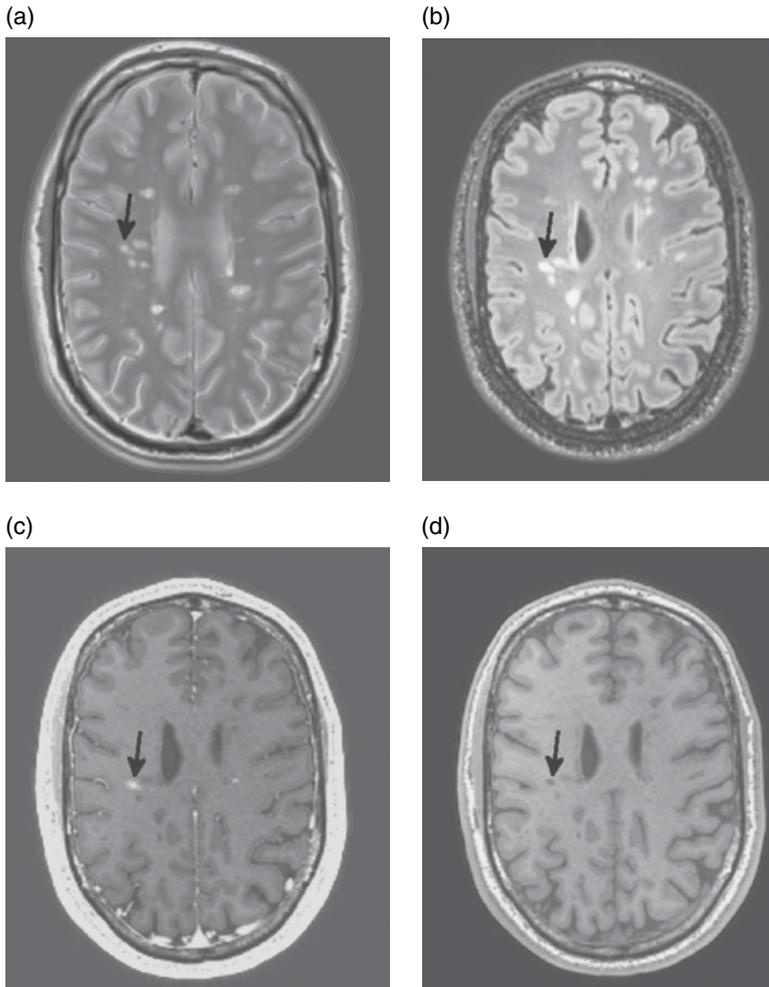
Figure 4.1 Brain images of a 43-year-old man with active relapsing–remitting MS, performed on a 3 T scanner. (a) Proton density. (b) T2-FLAIR. (c) T1 without contrast. (d) T1 after injection of 0.1 mmol/kg gadobutrol. The arrows denote an enhancing lesion that was not present on the prior scan 1 month earlier. Note that the plane of section for the proton density image (a) is slightly different from that of the other images.

☆ **TIPS AND TRICKS**

- Atrophy is profound in long-standing MS and begins early in the disease.
- Other diseases cause lesions in T2 images that may mimic MS. The presence of spinal cord lesions and veins in the center of most MS lesions (seen best on susceptibility or T2* images) makes MS much more likely.

gadolinium. These changes in signal intensity reflect resolution of edema, clearance of cellular debris, remyelination, and gliosis.

Lesion location

Brain lesions are commonly periventricular, juxtacortical (at the gray–white junction), and infratentorial (including brainstem and cerebellum), but they can occur anywhere. White matter lesions tend to have an ovoid configuration, to occur along the callososeptal interface, and to extend outward from the bodies of the

lateral ventricles along the deep medullary veins (forming the so-called Dawson's fingers). White matter lesions may also extend into the gray matter, including both cortex and deep nuclei (particularly the thalamus). Lesions may also develop directly within the gray matter; these lesions have been classified as either intracortical or subpial. Intracortical lesions are quite small and represent only about 10% of all cortical lesions. Subpial cortical lesions, which may represent 50% of the total seen in pathology studies, are not apparent in conventional MRI and are exceedingly difficult to detect reliably even in nonconventional MRI, although consensus guidelines for lesion identification using a technique called double inversion recovery (DIR) have been published (Geurts *et al.* 2011). Major reasons for the poor MRI contrast between normal gray matter and cortical lesions include partial volume effects (inclusion of multiple tissue types within individual voxels), less extracellular water, and the relative paucity of myelin compared to white matter.

Black holes

Lesions that are hypointense on T1-weighted spin-echo images are called *black holes* if they persist longer than 6 months, because they are thought to reflect areas of substantial tissue destruction (van Waesberghe *et al.* 1999). In fact, most newly formed lesions are T1 hypointense due to the presence of edema, but roughly 80% of these lesions become isointense (revert to the signal intensity of normal white matter) within a few months as the edema resolves and the damaged tissue partially repairs itself. Only approximately 20% of lesions remain hypointense after 6 months and meet the *black hole* definition (Bagnato *et al.* 2003). It is important to realize, however, that not all T1 images are alike, and many more lesions appear persistently hypointense on contemporary scans for technical reasons alone.

Contrast enhancement

Enhancement within an MS lesion indicates the presence of active inflammation and is the imaging correlate of a clinical relapse (although, as mentioned earlier, contrast-enhancing lesions occur much more commonly than relapses) (Katz *et al.* 1993). Contrast enhancement is usually a transient phenomenon in MS lesions, usually disappearing over 2–6 weeks but occasionally lasting longer. Lesion enhancement is less common in primary and secondary progressive MS. Old lesions may re-enhance if they reactivate, but it is often difficult to distinguish a re-enhancing lesion from a new lesion that develops adjacent to the old one. Enhancement may appear homogeneous throughout the lesion (the so-called *nodular* pattern), or it may appear only on the periphery (*ring* pattern). These differences may depend on the size of the lesion and the time interval between gadolinium injection and scan acquisition, rather than true differences in lesion biology (Gaitan *et al.* 2011).

Brain atrophy

Brain atrophy occurs in MS at a rate of about 0.5% per year, about two to three times more rapidly than in healthy people of similar age (De Stefano *et al.* 2010). In clinical practice, an easy, practical, qualitative method for assessing brain atrophy is to use an ordinal scale based on global assessment of ventricular size and sulcal width. On this scale, atrophy is described as mild, moderate, or severe (Simon *et al.* 2006). With image-processing software, the brain volume can be normalized to the size of the cranial vault to generate the *brain parenchymal fraction*, a useful cross-sectional estimate of brain atrophy in MS (Fisher *et al.* 2008).

✋ **CAUTION!**

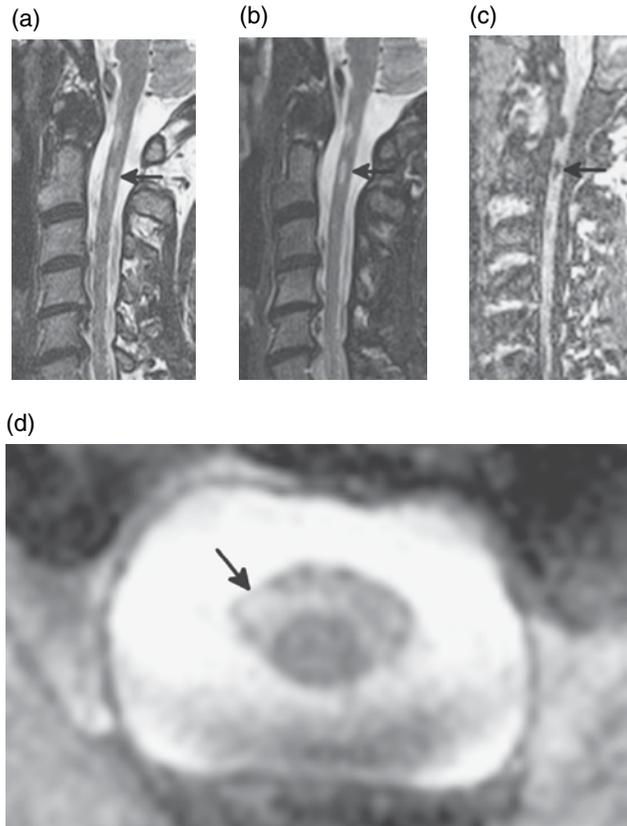*Question your diagnosis when you observe* the following:
- Normal MRI
- Substantial mass effect or displacement of nearby structures (rule out tumor)
- A lot of edema surrounding lesions (rule out tumor)
- Bleeding (rule out a vascular process)
- Symmetrically distributed lesions (rule out a toxic or metabolic process)
- Simultaneous enhancement of all lesions (rule out acute disseminated encephalomyelitis)

- Extensive leptomeningeal enhancement (rule out sarcoidosis and infections)
- Gray matter spinal lesions (rule out infarct)
- Long spinal cord lesions (rule out neuromyelitis optica)
- Enhancement lasting more than 3 months (rule out tumor)

Spinal cord

MS lesions are typically located in the posterior and lateral columns and, as in the brain, are for the most part multifocal and asymmetrically distributed. They develop in the periphery of the spinal white matter and are most frequently in the cervical spinal cord. They are usually less than one vertebral body in height and occupy less than half the cross-sectional area of the cord. By contrast, in neuromyelitis optica, lesions are usually much larger, typically more than three vertebral bodies in height. Spinal cord lesions are conventionally best detected in sagittal short-tau inversion recovery (STIR) images, but modern T1 and T2* imaging protocols show promise for improving detection of these often-hard-to-see lesions (Figure 4.2). As normal aging and small vessel disease do not typically cause spinal cord lesions, their presence is very useful for increasing diagnostic certainty. Thirty percent of patients with clinically isolated syndrome—often the initial presentation of MS—have asymptomatic spinal

Figure 4.2 Cervical spinal cord images of a 55-year-old woman with secondary progressive MS, performed on a 3 T scanner. (a) Sagittal T2. (b) Sagittal STIR. (c) Sagittal T1. (d) Axial T2* at the C1–C2 disk level. The arrows denote a lesion in the right lateral column on all images.

cord lesions, and 90% of patients with definite MS have cord lesions (Lycklama à Nijeholt *et al.* 2003). Spinal cord atrophy can be detected in any disease subtype, but it appears to be most severe in progressive MS. New spinal cord lesions enhance with gadolinium, but for technical reasons, such enhancement is more difficult to observe than in the brain.

MRI diagnostic criteria

The diagnostic criteria for establishing the diagnosis of MS are based on three main principles: (1) evidence of dissemination in time (DIT), (2) evidence of dissemination in space (DIS), and (3) exclusion of alternative diagnoses. In 2001, the International Panel on the Diagnosis of Multiple Sclerosis presented new diagnostic criteria, the so-called McDonald criteria, which for the first time integrated brain and spinal cord lesions detected by MRI with traditional diagnostic approaches (history, physical exam, and laboratory test). This new set of criteria was designed to be a straightforward diagnostic scheme to enable practicing neurologists to more reliably and consistently diagnose MS. They also allowed earlier diagnosis with a higher degree of specificity and sensitivity. In 2005, the revisions to the McDonald criteria simplified things further while maintaining adequate sensitivity and specificity.

The most recent revisions, formulated in 2010 and published in 2011, for the first time enabled the diagnosis to be made, in the context of an appropriate clinical presentation, on the basis of a single scan. This is accomplished by integrating knowledge about the time course of lesion enhancement into a determination of the presence or absence of both DIT and DIS (Polman *et al.* 2011). Thus, an MRI performed at any time that demonstrates DIS (more than one lesion) and that shows the simultaneous presence of nonenhancing and asymptomatic gadolinium-enhancing lesions is sufficient to support a diagnosis of relapsing–remitting MS. For DIS, the requirement is that one or more T2 lesions be present in at least two of four cardinal locations (periventricular, juxtacortical, infratentorial, and spinal cord). The appearance of a new T2 lesion on a follow-up scan, irrespective of the timing of the first scan, also fulfills criteria for DIT. The 2010 McDonald MRI criteria for both relapsing–remitting and primary progressive MS are reproduced in Table 4.1.

MRI consensus protocol

A standardized conventional MRI protocol has been proposed (Simon *et al.* 2006). In the brain, this protocol includes T1 images before and after contrast administration as well as proton density and T2 images (Table 4.2). For initial evaluation, a brain MRI study that mimics this standardized protocol should be acquired, and injection of contrast is strongly recommended. The standard dose of most gadolinium chelates, 0.1 mmol/kg, is based on a balance between safety, cost, and detection; however, in MS, it is clear that enhancement detection is higher with double and triple doses of contrast. The minimum delay for scanning is 5 min following the injection. Gadobutrol currently provides the best contrast between enhancing lesions and the background tissue (Lovblad *et al.* 2010). It is important to note that release of gadolinium ions from contrast agents appears to be relevant for the development of nephrogenic systemic fibrosis, a rare condition that occurs in patients with kidney failure and that is characterized by thickening and induration of the skin. Thus, contrast should only be administered in patients with potentially impaired kidney function when it is likely to affect clinical management, such as by uncovering an alternative diagnosis.

Spinal cord imaging may be useful if the main presenting symptoms can be localized to the spinal cord or if the results of the brain MRI are equivocal (Simon *et al.* 2006). However, artifacts related to cerebrospinal fluid flow and cardiac and respiratory motion may compromise evaluation of the spinal cord, and in practice, false positives and false negatives are quite common. The consensus recommendation for spinal cord MRI protocol is provided in Table 4.3.

Table 4.2 Consensus Brain MRI Protocol for Clinical Evaluation of MS

	Sequence	Diagnostic Scan for Clinically Isolated Syndrome	MS Baseline or Follow-up Scan	Comment
1	Three plane (or other) scout	Recommended	Recommended	Set up axial sections through subcallosal line[*]
2	Sagittal fast FLAIR	Recommended	Optional	Sagittal FLAIR sensitive to early MS pathology, such as in corpus callosum
3	Axial FSE PD/T2	Recommended	Recommended	TE_1 minimum (e.g., ≤30 ms) TE_2 (usually ≥80 ms) PD series sensitive to infratentorial lesions that may be missed by FLAIR series
4	Axial Fast FLAIR	Recommended	Recommended	Sensitive to white matter lesions and especially juxtacortical–cortical lesions
5	Axial pregadolinium T1	Optional	Optional	Considered routine for most neuroimaging studies
6	3D T1	Optional	Optional	Some centers use this for atrophy measure
7	Axial gadolinium-enhanced T1	Recommended	Optional	Standard dose of 0.1 mmol/kg injected over 30 s; scan starting minimum 5 min after start of injection

Source: Simon *et al.* (2006). Reproduced with permission of American Society of Neuroradiology. FSE indicates fast spin-echo (or turbo spin-echo); PD, proton density-weighted (long TR, short TE sequence); T1, T1-weighted (short TR, short TE sequence). Section thickness for sequences 3–6 is ≤3 mm with no intersection gaps when feasible. Partition thickness for 3D sequence 6 is ≤1.5 mm. In-plane resolution is approximately ≤1 × 1 mm.
*The subcallosal line joins the undersurface of the front (rostrum) and back (splenium) of the corpus callosum.

In general, the use of scanners with magnetic field strength equal to or higher than 1.5 T is strongly recommended in MS. Higher field strength increases the T1 relaxation time, providing better T1 images and better delineation of brain structures. Higher field strength also leads to improved image quality overall, with higher signal-to-noise ratio and the possibility of acquiring thinner sections in a reasonable scan time. At a minimum, we recommend acquiring 3 mm slices without gaps. When available, we prefer 3D sequences, in which data are acquired simultaneously from the whole brain rather than slice by slice, ideally using isotropic (cubic) voxels. T2-FLAIR images are generally acquired before gadolinium injection; however, in our experience, obtaining the T2-FLAIR images after gadolinium injection can improve the detection of enhancing lesions (Figure 4.3).

Table 4.3 Consensus Spinal Cord MRI Protocol for Clinical Evaluation of MS

When Acquired Immediately Following an Enhanced Brain MRI*		When Acquired without a Preceding Enhanced Brain MRI	
Sequence	Recommendation	Sequence	Recommendation
1 Three plane (or other scout)	Recommended	1 Three plane (or other scout)	Recommended
2 Postcontrast sagittal T1	Recommended	2 Precontrast sagittal T1	Recommended
3 Postcontrast sagittal FSE PD/T2†	Recommended	3 Precontrast sagittal FSE PD/T2†	Recommended
4 Postcontrast axial T1	Through suspicious lesions	4 Precontrast axial FSE PD/T2‡	Through suspicious lesions
5 Postcontrast axial FSE PD/T2‡	Through suspicious lesions	5 3D T1§	Optional
6 Postcontrast 3D T1§	Optional	6 Postcontrast-enhanced sagittal T1¶	Recommended
		7 Postcontrast-enhanced axial T1	Through suspicious lesion(s)

Source: Simon *et al.* (2006). Reproduced with permission of American Society of Neuroradiology.

FSE indicates fast spin-echo (or turbo spin-echo); PD, proton density-weighted (long TR, short TE sequence); T1, T1-weighted (short TR, short TE sequence); T2, T2-weighted (long TR, long TE sequence).

*Indications are (1) main presenting symptoms are at the level of the spinal cord, and these have not resolved; (2) if the brain MRI results are equivocal. No additional intravenous contrast is required if the spinal cord study immediately follows the contrast-enhanced brain MRI, as gain is very limited. The segment to be studied (cervical and/or thoracic) is based on clinical findings. Sagittal section thickness is 3 mm (no gap).

†PD series may depict lesions less apparent on heavily T2-weighted series.

‡Increases confidence in the findings of sagittal series; may provide classic lesion characteristics.

§For volumetric analysis if desired.

¶Standard dose of 0.1 mmol/kg injected over 30 s; scan starting 5 min after start of injection.
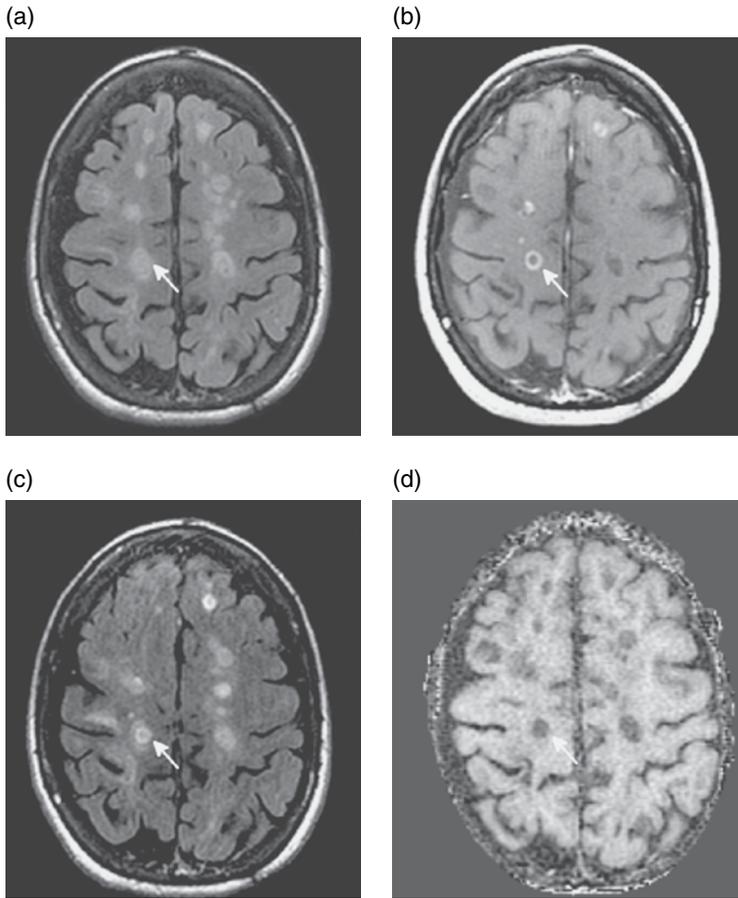
Figure 4.3 Brain images of a 51-year-old woman with active relapsing–remitting MS, performed on a 3 T scanner. (a) T2-FLAIR. (b) T1 after injection of 0.1 mmol/kg gadopentetate dimeglumine. Note the presence of four enhancing lesions, one of which is denoted by an arrow. (c) T2-FLAIR after contrast injection. Enhancing lesions are brighter than their nonenhancing counterparts. (d) MTR. Both enhancing and nonenhancing lesions are hypointense, probably due to a combination of demyelination and increased water content (edema).

MRI for monitoring disease and treatment

The primary goal of disease-modifying treatments in MS is to prevent the occurrence of new clinical relapses and ultimately disease progression. Since MRI is usually more sensitive to ongoing inflammation than clinical measures, MRI findings are often used as outcome measures to shorten phase I and II clinical trials of new MS therapies. Such outcome measures include the accumulation of new or enlarging T2 lesions, the presence of new contrast-enhancing lesions, change in the total lesion volume,

evolution of new lesions into *black holes*, and change in brain volume (Filippi & Rocca 2011). As discussed in the next section, advanced MRI techniques, such as magnetization transfer imaging, diffusion tensor imaging, and proton spectroscopy, can detect and quantify the extent of tissue damage inside and around lesions and can monitor how that damage changes over time.

In the clinic, follow-up MRI scanning is indicated when unexpected clinical worsening happens, for reassessment of disease burden prior to initiation of treatment, or when an alternative diagnosis is suspected (Simon *et al*. 2006).

Unfortunately, many of the changes detected by both conventional and advanced MRI are small and/or subtle, so it has been difficult to apply lessons learned from large populations in clinical trials, or in carefully controlled research settings, to the care of individual patients. Furthermore, interpretation of changes is difficult; an increase in lesion load in a patient under treatment may indeed reflect complete treatment failure, but it also could be the case that even more lesions would have accrued in the absence of treatment. Nevertheless, the standard of care in many centers is to acquire contrast-enhanced follow-up MRI scans to help in treatment decisions.

Since conventional MRI is highly sensitive to inflammation, if follow-up scans are performed carefully, meaning that imaging quality is high and patient positioning is similar, the radiological interpretation can provide very useful information about the evolution of the disease. The requirement for similar positioning will become less important as vendors integrate prospective scan alignment into their acquisition protocols and as registration techniques find their way into clinical image visualization software.

New lesion activity

Contrast is optional for follow-up studies, but it is exceedingly helpful as it allows determination of ongoing disease activity at the time of scanning. However, counting the number of contrast-enhancing lesions alone provides only a snapshot of disease activity. Although some new lesions may completely resolve, for the most part, new lesions permanently alter the local T2-weighted signal. Thus, detecting new or enlarging T2 lesions can provide information about ongoing disease activity over the interval since the previous scan. For this reason, a composite measure that integrates both contrast-enhancing lesions and new or enlarging T2 lesions has proved to be very useful in short- and long-term clinical trials for MS. Unfortunately, it is often difficult to find new T2 lesions, particularly if the lesions are small, data acquisition is not standardized, and the total lesion burden is high. Subtraction imaging is a relatively new and highly promising tool that may alleviate this difficulty (Moraal *et al.* 2010).

Brain atrophy

Brain atrophy reflects tissue loss and represents a global measure of both demyelination and axonal loss in MS. The number and volume of T2 lesions, as well as more subtle MRI-detectable abnormalities in extralesional white matter and gray matter, affect brain atrophy. Quantitative atrophy estimation, involving postprocessing by automated or semiautomated methods, can detect progressive loss of brain volume and, in particular, the gray matter atrophy that appears to most strongly drive whole-brain atrophy (Fisher *et al.* 2008). Disease-modifying therapies can reduce brain atrophy, although after the initiation of treatment, care must be taken not to interpret an initial drop in brain volume (sometimes called *pseudoatrophy*) that is thought to be due to a reduction in inflammation. How to integrate brain volume measurement (which commonly varies substantially across scanners and scan acquisition parameters) into clinical practice is an ongoing area of research.

Limitations

The limitations of conventional MRI for disease monitoring include the weak associations with clinical status and the relatively poor sensitivity to some clinically relevant findings, such as gray matter disease and diffuse damage throughout the white matter. In addition, serial spinal MRI reveals only one-tenth as much activity as brain MRI in relapsing–remitting MS; whether this reflects differences in lesion accumulation or technical factors (poorer imaging) remains unclear.

Nonconventional MRI

The correlation between the lesion volume observed on conventional MRI and the clinical burden of disease is far from perfect. Possible explanations for this so-called clinical–radiological paradox include limited specificity for

the pathological substrates of MS, difficulties in quantifying the extent of damage to extralesional white matter areas (the so-called normal-appearing white matter or NAWM), lack of sensitivity to gray matter lesions, variability of clinical expression of MS lesions in different areas of the brain, and the relative insensitivity of clinical disability scales, especially with respect to cognition. Advanced MRI techniques have begun to alleviate some of these issues because they can provide insight into the underlying pathology as well as the mechanisms of disease evolution and treatment response. However, the application and interpretation of these techniques in clinical practice and clinical trials remain a matter of intense research interest. See Science Revisited for information on specific techniques; their clinical relevance is discussed later.

Magnetization transfer imaging

This technique enables calculation of a semi-quantitative index, the *magnetization transfer ratio* (MTR). Low MTR can be caused by demyelination and axonal loss as well as edema and inflammation, particularly in newly forming lesions (Figure 4.3). Subtle decreases in MTR can be retrospectively detected in the weeks and months prior to lesion formation (Pike *et al.* 2000). A persistent increase of MTR following an initial decrease may indicate remyelination (Giacomini *et al.* 2009). Published experience with magnetization transfer imaging in clinical trials is so far limited, but it holds some promise in this regard.

Magnetic resonance spectroscopy

Spectroscopy is usually performed in single voxels but can also be acquired in entire slices via a technique known variously as chemical shift or spectroscopic imaging. Enhancing lesions may show elevated choline, which reflects ongoing synthesis and breakdown of membranes (in white matter, mostly myelin); the choline level returns to normal over a 4–6-month period. Transiently elevated lactate may reflect altered metabolism within enhancing lesions. The most prominent change in MS lesions, however, is a decrease in the concentration of NAA, which may normalize after a few months or remain persistently low (Davie *et al.* 1994). Global NAA, measured across the whole brain, is also abnormally low in MS. Because NAA is detected almost exclusively in neurons and their processes, decreases in this metabolite can be interpreted as evidence of axonal injury. NAA levels correlates with axonal density and disability as measured with EDSS (Bjartmar *et al.* 2000).

Susceptibility-weighted imaging

Venous abnormalities and iron deposition in the MS brain are two topics of current interest. MS lesions develop around small parenchymal veins, and this can be directly demonstrated using T2* (or susceptibility) weighting (Figure 4.4b). Detection of veins is markedly improved at higher magnetic field strengths and can be accomplished at 3 and, even more effectively, at 7 T (Tallantyre *et al.* 2009). This type of imaging also demonstrates a hypointense peripheral rim around approximately 10% of MS lesions, which appears to correlate with iron accumulation in macrophages in the periphery of chronic active lesions (Pitt *et al.* 2010). As it is sensitive to some of the tissue changes that appear to be most relevant for the pathophysiology of MS, this technique may open a new window into the mechanisms of lesion development and evolution.

Diffusion-weighted imaging

Demyelination, remyelination, and neurodegeneration may produce abnormal water motion and thereby change measures of diffusion in tissue, to which MRI is sensitive. The total extent of diffusion, quantified as the mean diffusivity or apparent diffusion coefficient, is often especially high in contrast-enhancing and T1-hypointense lesions (Figure 4.4c) (Rovaris *et al.* 2005). However, transient decreases in mean diffusivity sometimes occur in acute MS lesions, especially in the optic nerve; this may reflect swelling of the myelin sheaths, cytotoxic edema, or intense inflammatory cell infiltration. Directional diffusion may also be measured using a technique known as diffusion tensor imaging. In addition to

(a)

(b)

(c)

(d)
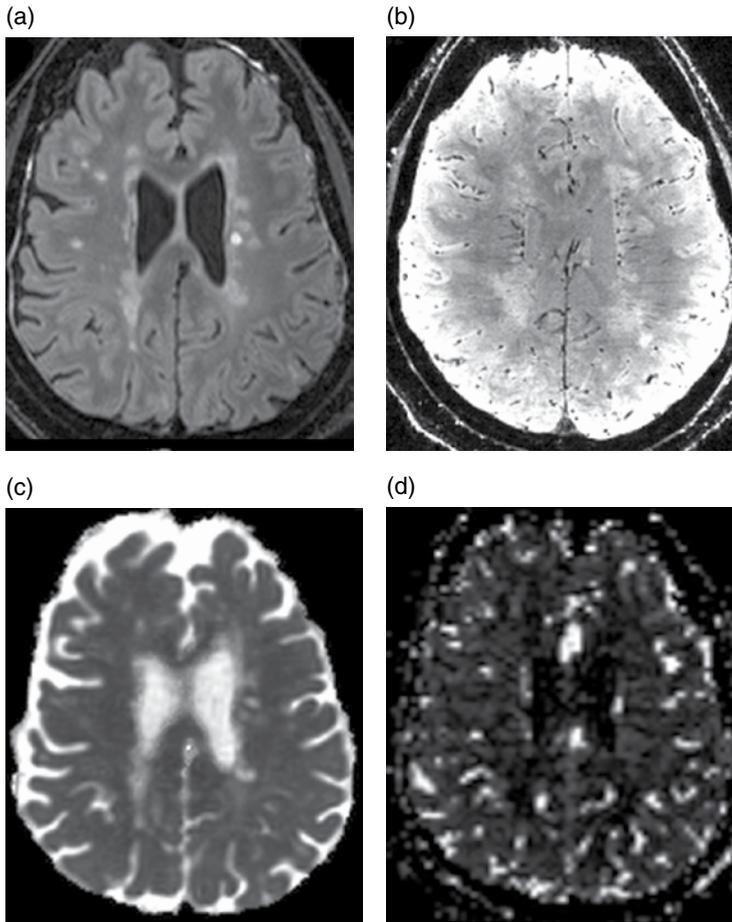
Figure 4.4 Brain images of a 64-year-old woman with primary progressive MS, performed on a 3 T scanner. (a) T2-FLAIR after injection of 0.1 mmol/kg gadobutrol showing an enhancing periventricular lesion. (b) T2* (susceptibility) image showing the presence of a vein (arrow) within the lesion. (c) Mean diffusivity map showing facilitated diffusion of water within the enhancing lesion. (d) Relative cerebral blood volume map showing elevated perfusion within the enhancing lesion.

allowing reconstruction of various white matter pathways, directional diffusion may in some situations help to distinguish axonal damage from other concurrent pathologies, although this is rarely the case in MS.

Perfusion-weighted imaging

Perfusion can be estimated by a variety of MRI techniques. Increased local perfusion can be detected in acute lesions (Figure 4.4d), and this finding may even precede lesion appearance on T2 images (Wuerfel *et al*. 2004). In chronic lesions and gray matter, perfusion is abnormally low, a

finding that remains unexplained at present (Ge *et al*. 2005). Indeed, the overall relationship between blood flow and MS pathogenesis remains a topic of intense current interest.

Conclusions

In the three decades since it was introduced as a clinical tool, MRI has become the cornerstone diagnostic tool in MS and, as such, an indispensible part of patient care. Scientifically, it has opened up new avenues in MS research and enabled more rapid, precise testing of new drugs. With continued rapid evolution of the technology,

some of the pathological and pathophysiological processes that were previously visible only under the microscope or in the test tube will become accessible to routine, noninvasive monitoring.

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