A 40-year-old female patient, known to be suffering from multiple sclerosis, was presented clinically with painful diminution of vision in the right eye and mild weakness of the left upper limb.

Figure 1. A case of chronic multiple sclerosis. MRI T1 precontrast images showing multiple periventricular oval or rounded plaques. The plaques are well-defined, hypointense to markedly hypointense (black holes) with mild central atrophy. Some plaques are perpendicular to the ventricular surface (Dawson fingers). T1 hypointensities serve as a surrogate marker of disability in multiple sclerosis because they are specific for matrix destruction and axonal loss. Development of T1 hypointensities implies not only focal damage to axons within lesions, but also more widespread tissue loss, leading to generalized atrophy of the brain.
Figure 2. Postcontrast MRI T1 images showing contrast enhancement of multiple sclerosis plaques. Two patterns are seen. Diffuse contrast enhancement (A) and ring enhancement (either complete ring enhancement or incomplete ring enhancement, both patterns are seen in this patient) (B,C). Enhanced plaques are active plaques and is a manifestation of disease exacerbation even when not associated with clinical manifestations. Ring enhancement demonstrates how MRI can show dissemination in time as well as place. Plaques with ring enhancement are plaques with different ages. The central unenhanced parts are older than the peripherally enhanced parts. Reactivation of old plaques takes place at the periphery of plaques and that explains ring enhancement. Plaques with ring enhancement represent dissemination in time. Non enhanced plaques are plaques in remission while enhanced plaques are plaques in exacerbation. Plaques with ring enhancement are plaques which contain central parts in remission and peripheral parts in exacerbation. The open, incomplete, ring enhancement that is seen in the cerebellum in this patient (B) is more indicative of an MS lesion than metastatic disease or infection which almost always has a complete, fully enclosed ring of enhancement.

Figure 3. A case of chronic multiple sclerosis. MRI T2 (A,B) and MRI FLAIR (C) images showing multiple periventricular oval or rounded plaques. The plaques are well-defined and hyperintense. Some plaques are perpendicular to the ventricular surface (Dawson fingers).
• The existence of dissemination in place: MRI plaques that are widespread within the brain, in the periventricular regions. Some plaques are perpendicular to the ventricular surface (Dawson fingers). In particular Dawson fingers are rarely seen in other white matter diseases.

• The existence of dissemination in time: As manifested by some plaques showing contrast enhancement (active plaques) and other are not enhanced (chronic inactive plaques). Ring enhancement in a single plaque is also a sign of dissemination in time.

Multiple sclerosis is characterized by dissemination in time and place. Dissemination in time and place (either clinically or by MRI) is not seen in other white matter diseases.

While commenting on a neuroimaging study for a multiple sclerosis patient, four parameters must be commented upon. The anatomical distribution of the lesions, The presence or absence of brain atrophy, T2 and FLAIR appearance of the lesions and the appearance of the lesions on the pre and postcontrast T1 images.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Anatomy</td>
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<tr>
<td>Atrophy</td>
<td>With an extensive lesion burden, marked atrophy may be present. The corpus callosum may be severely thinned throughout. To what extent the atrophy represents primary white matter disease or secondary loss due to Wallerian degeneration is not clear.</td>
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| T1 pre and postcontrast | Initially, MS lesions are isointense to mildly hypointense on T1-weighted imaging. With time, the mild hypointensity may progress to develop into a so-called T1 hole or black hole in which the lesion has completely been replaced by CSF. Alternatively, the lesion may remain stable in intensity. In many cases, there is a slightly hyperintense rim surrounding a lesion. This hyperintensity is typically ascribed to the presence of free radicals in the surrounding inflammatory tissue, but paramagnetic effects from petechial hemorrhage and fat signal from myelin breakdown also may contribute to this phenomenon. T1 hypointensities serve as a surrogate marker of disability in multiple sclerosis because they are specific for matrix destruction and axonal loss. Development of T1 hypointensities implies not only focal damage to axons within lesions, but also more widespread tissue loss, leading to generalized atrophy of the brain. Contrast enhancement represents a disruption in the blood-brain barrier that allows for the leakage of gadolinium-chelates. The presence of enhancement can play an important role in the evaluation of MS, depending on the clinical context. Enhancement results from a local breakdown of the blood-brain barrier, and indicates the presence of an active inflammatory process; therefore, enhancement identifies "active lesions," which often correlate with the acute symptomatology. These active lesions also may be clinically silent and are frequently seen on serial imaging performed as part of research protocols. Because nonenhancing lesions identified on T2-weighted images are thought to be chronic lesions, the simultaneous presence of enhancing and nonenhancing lesions is strong evidence to indicate that these are "multiple
DIAGNOSIS: A CASE WITH CHRONIC MULTIPLE SCLEROSIS IN EXACERBATION BY CLINICAL AND MRI CRITERIA

DISCUSSION

Multiple sclerosis (MS) is a histopathologic diagnosis manifesting clinically as neurologic signs and symptoms disseminated in time and space. The Poser et al criteria established the important role of paraclinical tests in establishing the diagnosis of MS. Magnetic resonance (MR) imaging has proven to be the dominant paraclinical test in establishing the diagnosis of MS, showing multiple white matter hyperintensities on T2-weighted images in more than 90% of patients. The sensitivity of MR imaging is emphasized by longitudinal studies that demonstrate five to ten times more lesions than might be expected from overt clinical relapses.

Because MR imaging can be used to survey the entire neuraxis, it is able to identify these clinically silent lesions, thus establishing the presence of multiple lesions in space. Furthermore, as lesions enhance only when they are relatively acute, (typically < 2 months), enhancement or lack thereof dates a lesion; hence, the presence of enhancement provides temporal and anatomical information. That is, a single MR image with enhancing and nonenhancing lesions may be interpreted as having lesions separated in time. Thus, MR imaging is uniquely suited to provide information on white matter lesions distributed in time and space. Not to be overlooked is the strength of MR imaging in establishing or ruling out other diagnoses at the time of initial presentation.

Although MR imaging is a sensitive technique for detecting lesions, it is hampered by its lack of specificity. Most insults to the brain, demyelinating disease included, increase water content because of edema and gliosis, prolonging tissue T2 relaxation time. Thus, lesions are hyperintense on sequences sensitized to the T2 relaxation time, namely, proton density (PD)-weighted, T2-weighted, and fluid attenuated inversion-recovery (FLAIR) sequences, both in their conventional spin-echo (CSE) and fast spin-echo (FSE) implementations.

Because of this lack of specificity, arriving at a correct clinical diagnosis depends to a great extent on characterizing the anatomic configuration of the injury in the white matter, and the correlation of these findings with clinical data.

MR IMAGING APPEARANCE OF MS LESIONS

- Anatomic Distribution

MS lesions are typically nodular or ovoid in appearance, and range in size from several millimeters to more than 1 centimeter. The lesions have a propensity for large white matter tracts, particularly the corpus callosum, but involvement of white matter tracts in the brainstem (e.g., the medial longitudinal fasciculus and the middle cerebellar peduncle) is also characteristically observed in MS patients. In addition, juxtacortical lesions involving the U-fiber system are found, and these may extend into the gray matter of the cortex.

Usually, MS lesions extend along medullary veins that drain into the subependymal veins lining the lateral ventricle at the callososeptal interface. MS lesions are characteristically oriented along the fibers of the corpus callosum (although the veins themselves are not visible on routine MR imaging) paralleling these veins. This appearance corresponds to the so-called Dawson's finger identified at pathology (Fig. 4b), and is well demonstrated on MR imaging (Fig. 4a). Whereas the typical MS lesion is pericallosal or periventricular in location, they may involve any portion of the white matter, and can extend into the involved gray matter as well.
Figure 4a. Classic ovoid nodular MS plaques in a Dawson's finger configuration oriented parallel to the white matter tracts. Note the black hole appearance of many of the plaques on the T1 MRI image and the thin rim of T2 hyperintensity. A=spin-echo (SE) T1 B =proton density, C=T2 weighted SE

Figure 4b. MS lesions are characteristically oriented along the fibers of the corpus callosum (although the veins themselves are not visible on routine MR imaging) paralleling these veins. This appearance corresponds to the so-called Dawson's finger identified at pathology

Identification of lesions at the callososeptal interface is, therefore, thought to represent a characteristic finding in MS, having high sensitivity and specificity (93% and 96%, respectively). This may be seen as "notching" on the undersurface of the corpus callosum on sagittal T1-weighted imaging. Recently, a subtler "subcallosal striation" has been described using thin-section (2 mm) sagittal FLAIR sequences. These subtler lesions may be similarly sensitive (94%), although not as specific (84%). These striations are thin white lines radiating away from the callososeptal interface, presumably representing the earliest manifestations of MS in this location (Fig. 5).

In contrast to small vessel ischemic changes, MS lesions tend to be more discrete and well defined, becoming confluent only with severe disease progression.

Occasionally, MS lesions present as large lesions with mass effect (tumefactive MS) and vasogenic edema, indistinguishable from a brain tumor by MR imaging. Even a small lesion with enhancement may appear identical to a tumor, metastasis, or abscess.

- Other Imaging Findings in MS
With an extensive lesion burden, marked atrophy may be present (Fig. 6). The corpus callosum may be severely thinned throughout. To what extent the atrophy represents primary white matter disease or secondary loss due to Wallerian degeneration is not clear.

Diffuse white matter abnormality also may be present. This occasionally appears on routine MR imaging as "dirty white matter," which has diffusely increased T2 signal throughout (Fig. 7). This may be difficult to distinguish from normal variation of myelination, and familiarity with the appearance of white matter on the particular scanner is essential to confidently identify this appearance.

Figure 5. Thin section (2 mm) sagittal fluid attenuated inversion-recovery (FLAIR) images from lateral to medial (A-C) in a patient with a diagnosis of optic neuritis. The presence of subcallosal striations can be seen as thin hyperintense bands radiating from the undersurface of the callosum. This sign is highly predictive of developing clinical MS.

Figure 6. Atrophy in a 26-year-old woman with MS. Note the marked thinning of the corpus callosum on the midline sagittal T1-weighted image (A). Relatively confluent white matter disease is present. B, FLAIR image shows the frontal horns in particular are enlarged.
Figure 7. Extensive confluent white matter involvement in MS. Extent of dirty white matter appearance is seen to greater advantage on FLAIR (A) than on fast spin-echo (FSE) T2-weighted sequence (B). Discrete nodular lesions are clearly seen against the background white matter abnormality on FSE PD weighted images (C) but are not seen as well on FLAIR or FSE T2-weighted images. No black holes are identified on SE T1-weighted images (D), but numerous punctate enhancing lesions are seen following contrast administration (E). The enhancement must be evaluated against a background of hyperintense white matter when magnetization transfer is used after contrast (F).

With progression of disease, non-heme iron deposition in the basal ganglia is greater than that seen in the normal populations. This deposition of ferritin in the basal ganglia is not specific to MS but may be found in a number of degenerative processes in the brain.

- **Signal Intensity Characteristics of MS Lesions**
  - **Proton Density and T2-Weighted Signals**

  Increased water content of tissue leads to an increase in the tissue T2 relaxation time. This results in hyperintense signal on FLAIR, PD- and T2-weighted imaging. Because most pathologic processes lead to increased tissue water, initially through edema and inflammation, and later through gliosis and frank replacement of tissue with fluid, T2 imaging is a sensitive but not particularly specific indicator of pathology. Conventional SE PD- and T2-weighted images were initially demonstrated to be highly sensitive for MS. In the last decade, FSE techniques have largely replaced CSE techniques, largely because of shorter acquisition times. Image contrast is similar between FSE and CSE techniques, with similar sensitivities for lesion detection.

- Consistent with pathologic observations, the classic MR imaging appearance of MS is one of multiple hyperintense white matter lesions with periventricular predominance. An important limitation of MR imaging is the low pathologic specificity of these hyperintense lesions. MS plaques are readily seen on PD and T2-weighted sequences because they have a higher proton density and longer T2 relaxation times than
normal white matter; however this is equally the case for other pathologies whether infarcts, infections, other inflammatory conditions, and tumors. Furthermore any of the main pathologic features of the MS plaque itself may result in a similar hyperintense appearance. It occurs in new lesions because of the inflammatory edema associated with blood-brain barrier (BBB) breakdown. In chronic lesions, it may be the result of an increase in extracellular fluid associated with demyelination and axonal loss or to gliosis (fibrous astroglisis) that may increase intracellular water content. Demyelination itself, with the breakdown of the fatty myelin sheaths within the MS lesion, probably does not contribute significantly to the prolonged T2 relaxation changes. The amount of lipid lost is not large enough to cause the magnitude of change demonstrated on MR imaging because the lipids related to myelin breakdown have an extremely short T2 relaxation time and are effectively invisible on conventional MR imaging. The loss of myelin lipid does, however, result in a more hydrophilic environment, and this increase in water content leads to the observed increases in proton density, T1, and T2 relaxation times.

- **Gliosis (fibrous astroglisis)** is important for the T2 signal in chronic lesions and the neutral fat resulting from demyelination per se is unlikely to make a contribution to the MR signal, whereas presumably the water that replaced the lipid lost by demyelination did. The T2 signal in acute lesions is likely caused by edema.

**Fluid Attenuated Inversion-Recovery**

Inversion-recovery techniques Suppress signal by placing an inversion pulse a certain time interval before image acquisitions. Tissues with a T1 approximately 1.5 times this inversion time will have their signal suppressed. Short inversion times will suppress fat, and long inversion times will suppress water. The FLAIR technique uses inversion times on the order of 2 seconds to suppress signal from free fluid, namely, cerebrospinal fluid (CSF). The inversion is followed by a T2-weighted imaging sequence. The resulting image is heavily T2-weighted, with signal from free fluid (i.e., CSF) nulled. By suppressing CSF signal from the ventricles and subarachnoid spaces, the conspicuity of T2 hyperintense white matter lesions is markedly enhanced, particularly in the periventricular regions where MS lesions are most characteristically seen.

In its original implementation, FLAIR imaging was time consuming. Fast FLAIR uses FSE techniques to achieve clinically reasonable imaging times. 63 Using this sequence, the conspicuity of lesions near CSF, namely, periventricular and juxtacortical lesions, is markedly enhanced resulting in identification of many more lesions than on CSE or FSE techniques. 77

Because of this, FLAIR is the sequence of choice in identifying supratentorial white matter lesions. Unfortunately, FLAIR has proven to be less sensitive than PD- and T2-weighted imaging in the infratentorial compartment (Fig. 8). 45,77 Because FLAIR uses inversion recovery, some T1 effects are present, and it may be that these T1 effects counter the T2 effects in the brainstem and cerebellum. Because of these different T1 relaxation times, it is possible that a modification of the standard inversion times used for FLAIR may be necessary. Similar findings have been shown in the spinal cord, where FLAIR also is relatively insensitive. 28 Thus, in many situations, it may be prudent to use FLAIR, PD, and T2 sequences to fully evaluate the intracranial compartment.

**T1 Properties**

Initially, MS lesions are isointense to mildly hypointense on T1-weighted imaging. With time, the mild hypointensity may progress to develop into a so-called T1 hole or black hole in which the lesion has completely been replaced by CSF (Fig. 9). 75

Alternatively, the lesion may remain stable in intensity. In many cases, there is a slightly hyperintense rim surrounding a lesion. This hyperintensity is typically ascribed to the presence of free radicals in the surrounding inflammatory tissue, but paramagnetic effects from petechial hemorrhage and fat signal from myelin breakdown also may contribute to this phenomenon. 58 The appearance of a T1 hyperintense ring around a T1 hypointense lesion is fairly characteristic of MS but may be seen with any inflammatory process, such as abscess formation. 22

- T1 hypointensities serve as a surrogate marker of disability in multiple sclerosis because they are specific for matrix destruction and axonal loss. Development of T1 hypointensities implies not only focal damage to axons within lesions, but also more widespread tissue loss, leading to generalized atrophy of the brain.
A TI hypointensity is defined as an area on a conventional SE (short TR/short TE) T1- weighted image that is hypointense compared with surrounding white matter (in this case referred to as normal-appearing white matter [NAWMI] and cortex, and is accompanied by an equivalent hyperintense area on a T2-weighted image.

Hypointense lesions usually begin as focal enhancements on postcontrast T1- weighted images (with accompanying hyperintensity on T2-weighted images) and most will be hypointense in the acute stage on precontrast T1-weighted images. Later, they can resolve and become isointense on precontrast T1-weighted images or remain hypointense (but always stay hyperintense on T2- weighted images). These changes in appearance take place in the first 2 months of lesion evolution and remain unchanged thereafter.

Sequence of events in the development of a black hole. After a lesion has enhanced on T1-weighted imaging, it frequently goes through a transient hypointensity stage (seen on precontrast T1 -weighted MR imaging), which may be determined only by temporary edema in and around the lesion area. The subsequent course of the hypointensity is unknown at this starting point; it might develop into a permanent hypointensity (chronic black hole), or it might recover partially (remyelination and axonal survival), and become a gray lesion. In the best-case scenario, it will resolve completely and become isointense to surrounding white matter (temporary black hole). This does not apply for T2-weighted images; they will remain bright. TI hypointensities should not be thought of simply as the sole areas of destruction, but rather as indicators of an underlying destructive process.

TI hypointensities is a marker of severe tissue damage and axonal loss, even early in the disease course. Although it is unlikely that axonal loss per se contributes to the appearance of the lesions on T1-weighted images, it is indeed an invariably associated finding. Most probably axonal loss is connected to the development of hypointensity through the accompanying increase in extracellular fluid.

Four lesion stages were distinguished according to neuropathologic criteria and matched to the T1-weighted images: early active lesions, which appeared isointense or slightly hypointense on T1- weighted images and with extensive gadolinium (Gd) enhancement; late active lesions, which were weakly hypointense or severely hypointense on T1-weighted images and with variable Gd enhancement; demyelinated lesions, which were clearly hypointense on T1- weighted images and with variable Gd enhancement; and remyelinating lesions, which emerged as weakly hypointense on T1 -weighted images with variable Gd enhancement. All lesion types except early active were hyperintense on T2-weighted images. The degree of axonal loss was correlated with the degree of lesion hypointensity.

MS lesions on T2-weighted images are nonspecific for the neuropathologic substrate, and could represent old lesions that are demyelinated, partly or highly remyelinated, new lesions, gliosis, and axonal loss. Therefore T2-weighted lesions are bound to have a poor correlation with the expanded disability status scale (EDSS). Since hypointensity on T1-weighted imaging is a marker of axonal loss, one would expect a better correlation with disability. Indeed, cross-sectional studies show higher correlation compared with T2- weighted images.

The occurrence of TI hypointensities can be used to differentiate small vessel ischemic lesions from MS. The occurrence of TI hypointensities is typical for MS but not for ischemic white matter lesions. Unfortunately, the number of TI hypointensities at first presentation is low, indicating that the high specificity of this finding in the very early phases of the disease is offset by a low sensitivity.
Figure 8. Infratentorial lesion in the left pons is visualized best on the FSE PD-weighted sequence (A). FSE T2-weighted (B) and FLAIR images (C) show poorer lesion-to-background contrast.

Figure 9. Juxtacortical T1 black hole, with rim of hyperintensity on T1-weighted image (A), with otherwise typical findings on FSE PD-weighted (B), FSE T2-weighted (C) and FLAIR (D) images. Note that incidental white matter lesions are virtually always isointense on T1-weighted images.

Contrast Enhancement

Contrast enhancement represents a disruption in the blood-brain barrier that allows for the leakage of gadolinium-chelates. The presence of enhancement can play an important role in the evaluation of MS, depending on the clinical context. Enhancement results from a local breakdown of the blood-brain barrier, and indicates the presence of an active inflammatory process; therefore, enhancement identifies "active lesions," which often correlate with the acute symptomatology. ²⁷¹ These active lesions also may be clinically silent and are frequently seen on serial imaging performed as part of research protocols.

Because nonenhancing lesions identified on T2-weighted images are thought to be chronic lesions, the simultaneous presence of enhancing and nonenhancing lesions is strong evidence to indicate that these are "multiple lesions separated in time," supporting a putative diagnosis of MS at the time of initial presentation.

The presence of ring-enhancement suggests the reactivation of an old lesion-the central nonenhancing portion of the lesion representing the "burnt out" portion of the lesion. An incomplete or open ring of enhancement is more indicative of an MS lesion than metastatic disease or infection, which almost always has a complete, fully enclosed ring of enhancement. ³⁷

Detection of enhancing lesions may be increased by a number of techniques, including decreasing slice thickness, use
of triple-dose gadolinium, application of magnetization transfer (MT), and acquiring delayed images. The clinical value of these techniques must be weighed against the additional costs of contrast material, imaging time, and false-positive findings.

- **Magnetization Transfer**

MT is used in combination with T1-weighted imaging to suppress signal from bound protons. This combination suppresses signal from white matter to a greater degree than gray matter and thus reduces gray-white contrast. Signals from MS lesions suppress less than normal white matter with MT and therefore are somewhat hyperintense on T1-weighted imaging.

In the context of MS, the detection of a new enhancing lesion is an indicator of disease activity. In standard T1-weighted imaging, chronic lesions usually are isointense to hypointense, relative to the background of white matter. Therefore, a new enhancing lesion is relatively easy to detect, because of the high contrast between new and old lesions. With MT, chronic lesions and the abnormal white matter background become hyperintense. Detection of enhancement requires careful comparison of pre- and postcontrast images to avoid over-interpreting hyperintensity as contrast enhancement. Thus although MT clearly plays a research role in the quantification of white matter disease, the ability to detect a new solitary lesion may be performed best by standard T1-weighted imaging.

- **Diffusion-Weighted Imaging**

Diffusion-weighted imaging has revolutionized MR imaging of stroke by acutely demonstrating cytotoxic edema. Diffusion-weighted sequences reliably differentiate vasogenic and cytotoxic edema. Recent explorations of diffusion-weighted imaging in MS show that subtle vasogenic edema can be identified before the development of an enhancing lesion.

- **Temporal Characteristics**

Evolving MS lesions have a characteristic temporal profile demonstrable on T2-weighted sequences. They reach a maximum size in approximately 4 weeks, before gradually shrinking, usually leaving a small residual abnormality indistinguishable from chronic MS lesions.

The course of contrast enhancement is similar. Only 25% of enhancing lesions are found to enhance 1 month after initial identification. Six months later, essentially no lesions enhance.

Retrospective analysis of serially imaged patients suggests that subtle MT and diffusion abnormalities precede the development of new lesions. This indicates that breakdown of the blood-brain barrier precedes the development of the inflammatory plaque.

It is unclear what factors result in axonal loss and the formation of a T1 black hole. The extent of enhancement at the initial presentation of a lesion correlates poorly with eventual T1 and T2 lesion burden. The burden of T1 hypointensity correlates with disability to a much higher degree than the T2 lesion load, indicating that the axonal loss or destruction is more directly related to neural dysfunction than demyelination alone.

- Because MR imaging can be used to survey the entire neuraxis, it is able to identify these clinically silent lesions, thus establishing the presence of multiple lesions in space. Furthermore, as lesions enhance only when they are relatively acute, (typically < 2 months), enhancement or lack thereof dates a lesion; hence, the presence of enhancement provides temporal and anatomical information. That is, a single MR image with enhancing and nonenhancing lesions may be interpreted as having lesions separated in time.

- MS lesions are typically nodular or ovoid in appearance, and range in size from several millimeters to more than 1 centimeter. The lesions have a propensity for large white matter tracts, particularly the corpus callosum, but involvement of white matter tracts in the brainstem (e.g., the medial longitudinal fasciculus and the middle cerebellar peduncle) is also characteristically observed in MS patients. In addition, juxtacortical lesions involving the U-fiber system are found, and these may extend into the gray matter of the cortex.

- Usually, MS lesions extend along medullary veins that drain into the subependymal veins lining the lateral ventricle at the callosal-septal interface. MS lesions are characteristically oriented along the fibers.
TECHNIQUES FOR EXAMINING WHITE MATTER

- **MR Imaging Sequences for Routine Clinical Examination**

Most MR imaging centers use a standard battery of sequences consisting of a sagittal T1, an axial FSE T2, and an axial fast FLAIR or FSE PD. Although the FLAIR sequence is attractive for many reasons, its inconsistency in evaluating the infratentorial compartment and the potential superiority of PD-weighted imaging may support the inclusion of FLAIR and FSE PD-weighted imaging in the evaluation. This is particularly true because infratentorial lesions, although less common than supratentorial lesions, tend to be more discrete and well defined, becoming confluent only with severe disease progression.

- Occasionally, MS lesions present as large lesions with mass effect (tumefactive MS) and vasogenic edema, indistinguishable from a brain tumor by MR imaging. Even a small lesion with enhancement may appear identical to a tumor, metastasis, or abscess.

- With an extensive lesion burden, marked atrophy may be present. The corpus callosum may become severely thinned throughout. To what extent the atrophy represents primary white matter disease or secondary loss due to Wallerian degeneration is not clear.

- Increased water content of tissue leads to an increase in the tissue T2 relaxation time. This results in hyperintense signal on PD- and T2-weighted imaging. Because most pathologic processes lead to increased tissue water, initially through edema and inflammation, and later through gliosis and frank replacement of tissue with fluid, T2 imaging is a sensitive but not particularly specific indicator of pathology.

- The FLAIR technique uses inversion times on the order of 2 seconds to suppress signal from free fluid, namely, cerebrospinal fluid (CSF). The inversion is followed by a T2-weighted imaging sequence. The resulting image is heavily T2-weighted, with signal from free fluid (i.e., CSF) nulled. By suppressing CSF signal from the ventricles and subarachnoid spaces, the conspicuity of T2 hyperintense white matter lesions is markedly enhanced, particularly in the periventricular regions where MS lesions are most characteristically seen. Because of this, FLAIR is the sequence of choice in identifying supratentorial white matter lesions. Unfortunately, FLAIR has proven to be less sensitive than PD- and T2-weighted imaging in the infratentorial compartment. Infratentorial lesions are more specific to multiple sclerosis than supratentorial lesions.

- The simultaneous presence of enhancing and nonenhancing lesions is strong evidence to indicate that these are "multiple lesions separated in time," supporting a putative diagnosis of MS at the time of initial presentation. The presence of ring-enhancement suggests the reactivation of an old lesion—the central nonenhancing portion of the lesion representing the "burnt out" portion of the lesion. An incomplete or open ring of enhancement is more indicative of an MS lesion than metastatic disease or infection, which almost always has a complete, fully enclosed ring of enhancement.

DIFFERENTIAL DIAGNOSIS OF WHITE MATTER DISEASE

- **Normal Variation and Small Vessel Ischemic Changes**

  - Virchow-Robin Spaces
Perivascular Virchow-Robin (VR) spaces represent extentions of subarachnoid space into the brain parenchyma along perforant vessels. These spaces are most often below the resolution of MR imaging, but they may be large enough to be confused with parenchymal lesions.

VR spaces often are found along the path of the lenticulostriate arteries that penetrate the basal ganglia through the anterior perforated substance in the neighborhood of the anterior commissure. These dilated spaces may be as much as 2 centimeters in diameter, at which point they often are confused with lacunar infarcts. 26, 35

VR spaces also may extend along the path of perforant medullary arteries traversing gray and white matter in the high convexities. Dilations of these spaces greater than 2 millimeters may be found in 8% of patients; here they are more likely to be confused with MS lesions. 2, 27

As VR spaces are extensions of the subarachnoid space, their signal follows that of CSF on all sequences. Careful attention to CSF signal may be necessary to distinguish a VR space from a true T2 hyperintensity. In particular, there is no halo of high signal gliosis on a FLAIR sequence around the dark CSF, as might be seen in a lacuna or a chronic MS lesion (Fig. 10). 44

- **Ependymitis Granularis**

Ependymitis granularis refers to the patchy loss of ependyma along the frontal horns with astrocytic gliosis, a nearly ubiquitous finding in MR imaging, and particularly noticeable on FLAIR sequences. The presence of high signal anterior to the frontal horns, and extending as a thin line along the bodies of the lateral ventricles, should not be misconstrued as pathology (Fig. 11). 70 In particular, the more globular and continuous appearance of ependymitis granularis should not be confused with subcallosal striations. 51

- **Incidental Hyperintensities and Small Vessel Ischemic Changes**

Punctate foci of T2 prolongation are seen in the white matter in otherwise healthy individuals. The incidence of these lesions increases with advancing age, so that by age 50, approximately 50% of the normal population will have such lesions with advancing age. 80

These hyperintensities rarely enhance. They tend to be found more in the subcortical and periventricular white matter. Juxtacortical white matter and the callososeptal areas are relatively spared, whereas the arterial watershed in the centrum semiovale is more directly affected 79; furthermore, small vessel ischemic changes are rarely hypointense on T1-weighted images (Fig. 12).

Infratentorial lesions are seen in the pons but rarely elsewhere. It is largely the presence of these incidental findings that reduces the specificity of MR imaging in establishing the diagnosis of MS.

- **Migraine**

Migraine is associated in some series with a higher incidence of T2 hyperintensities than in the normal population, with T2 hyperintense foci present in 40% to 45% of migraineurs. 31, 68 This is thought to be related to the abnormal vasoreactivity of cerebral vessels. Presumably, the same vascular hyperreactivity that is responsible for the migraine aura can lead to ischemia, resulting in foci of white matter gliosis. Other series, however, show no such elevation in the incidence of MR imaging hyperintensities. 50
Figure 10. Prominent Virchow-Robin space in the left parietal lobe. Note the isointensity to CSF on all sequences (A, FSE T2-weighted; B, FSE PD weighted; C, FLAIR; and D, SE T1-weighted images).

- **Vasculopathies**
  
  o **Immune-Mediated Vasculopathies**

As small vessel ischemia results in foci of white matter infarction, immune, nonimmune, and drug-induced vasculopathies can result in findings that mimic those of MS. The immune-mediated small vessel necrotizing vasculitides (e.g., Wegener's granulomatosis, micro polyangitis, and polyarteritis nodosa) have been associated with central nervous system (CNS) findings. 59 Collagen vascular diseases, particularly systemic lupus erythematosus and Behcet's disease, may manifest with white matter lesions. In lupus, large vessel infarctions are not uncommon. Behcet's disease is remarkable in the preponderance of brainstem abnormalities when CNS involvement occurs. 36

  o **Nonimmune Vasculopathies**

Nonimmune vasculopathies with a Mendelian inheritance pattern can give rise to small vessel ischemic changes. Examples of these entities include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and Fabry's disease.

CADASIL is a nonatherosclerotic, nonamyloid angiopathy affecting mainly the small penetrating arteries of the subcortical white matter and basal ganglia. In contrast to MS, basal ganglia involvement is greater and cortical U fibers are spared. 5

Figure 11. Ependymitis granularis outlining the lateral ventricles in a 71-year-old man. Incidental, scattered foci of T2 prolongation are present. Cerebrospinal fluid suppression renders these findings more conspicuously on the
FLAIR images (B and D) than on the FSE T2-weighted (A and C) images.

![FLAIR images](image)

**Figure 12.** Small vessel ischemic changes in a 79-year-old woman. Note that the larger lesions in the parietal white matter are not nodular or discrete. Ependymitis granularis is present, capping the frontal horns. (A, FSE T2-weighted; B, FLAIR; C, SE T1-weighted images.)

Fabry's disease is an X-linked recessive disorder of lipid metabolism, resulting from alpha-galactosidase A deficiency. Progressive accumulation of ceramidetrihexoside within the intima and media of cerebral blood vessels results in a typical small vessel ischemic pattern (Fig. 13). 7

![FLAIR images](image)

**Figure 13.** Fabry's disease. Adjacent FLAIR images through the corpus callosum demonstrate patchy lesions resulting from small vessel ischemia. Note the linear band of hyperintensity extending across the corpus callosum (B). Lesions here are atypical for small vessel ischemia, and may in this case represent Wallerian degeneration.

Many drugs of abuse have vasoactive effects that can lead to large or small vessel infarcts. Small vessel ischemia may be seen commonly with vasculitis related to cocaine and amphetamine addiction. 17

- **Infectious and Inflammatory Causes**
  - Neuroborreleosis

Lyme disease typically presents as an encephalopathy, which may be associated with a normal brain MR image; however, it can present as an MS-like illness with lesions indistinguishable from those of MS, so that differentiating between MS and Lyme disease cannot be based on imaging findings (Fig. 14). 23

  - Neurosarcoïdosis
Neurosarcoïdosis has protean manifestations and as such may present in a manner mimicking that of MS; however, more typical presentations of CNS sarcoïd effectively exclude MS. Densely enhancing basilar meningitis is a common presentation, often involving the neurohypophysis and cranial nerves. 65

- **Acute Disseminated Encephalomyelitis**

ADEM results from the cross-reaction of antibodies with myelin basic protein following a vaccination or viral infection. The pathophysiology is similar to that of MS, although ADEM is monophasic in course. No new lesions should develop several months after the initial ictus. Although multiple enhancing lesions may be seen at presentation, the lesions will follow the same time course of enhancement and should not enhance on subsequent MR scans. 36

- **Progressive Multifocal Leukoencephalopathy**

PML is a fatal papovavirus infection seen in the immunocompromised host. PML may present as a solitary lesion, although multifocal nonenhancing white matter lesions are more typically seen. Gray matter involvement and mass effect are unusual. The presence of mass effect is associated with a poor prognosis. The lack of enhancement was once considered a diagnostic requirement, but the presence of peripheral enhancement has been reported (Fig. 15). 57

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**Figure 14.** Lyme disease. FSE PD-weighted (A), FSE T2-weighted (B), and FLAIR (C) images demonstrate ovoid periventricular lesions mimicking those of MS. A juxtacortical left frontal lesion is seen clearly only on the FLAIR sequence (C).

**Figure 15.** Immunocompromised patient with biopsy-proven progressive multifocal leukoencephalopathy. Hyperintense lesion is seen in the left middle cerebellar peduncle on FLAIR (A) and T2-weighted (B) images. No
enhancement is seen following contrast administration (C and D). There is a suggestion of slight mass effect on the fourth ventricle, a poor prognostic sign. Note that these images were obtained after biopsy.

- **Human Immunodeficiency Virus**

HIV encephalopathy develops in up to 60% of HIV patients. T2 prolongation is found diffusely throughout the white matter. The abnormality is confluent, symmetric, and relatively homogeneous. Gray matter is spared, and enhancement is not seen. Atrophy develops in concordance with the white matter changes. Focal lesions are not seen, and it is not likely to be confused with MS (Fig. 16). 73

![Figure 16](image)

**Figure 16.** Spin-echo PD weighted (A) and SE T2-weighted (B) images showing diffuse, ill-defined, relatively symmetrical hyperintensity throughout the white matter in a patient with longstanding HIV, beginning to manifest dementia, presumably representing HIV encephalopathy.

- **Metabolic and Toxic White Matter Diseases**

  - **Reversible Posterior (Leuko)Encephalopathy Syndrome**

This entity refers to a fairly consistent clinical syndrome often seen with the development of acute hypertension, such as in eclampsia. It also is seen in the context of chemotherapy (typically with the use of cyclosporin), in transplantation or transfusion, with hypertension not clearly demonstrated. Clinically, seizures and visual disturbances are common presentations. The abnormalities may reverse with normalization of blood pressure and may or may not require discontinuation of the offending agent. 27

MR imaging demonstrates patchy regions of T2 prolongation in the periventricular and subcortical white matter in posterior parts of the brain, characteristically involving the white matter of the occipital and parietal lobes, but the cerebellum also may be involved (Fig. 20). Petechial hemorrhage may be seen on T2*-weighted imaging. The high signal primarily represents vasogenic edema and so is hypointense on diffusion-weighted imaging. Small foci of enhancement may be seen, and these may show high signal on diffusion-weighted imaging, indicating regions of irreversible damage. 54

- **Radiation-Induced White Matter Disease**

Neuropathologic consequences of therapeutic radiation include demyelination, microvascular occlusion, and blood-brain barrier breakdown. In a dose-dependent manner, white matter signal changes from patchy foci of T2 prolongation to confluence and finally to coagulative necrosis with blood-brain barrier breakdown. The posterior fossa, basal ganglia, and internal capsules are relatively spared (Fig. 21). 6, 76

- **Osmotic Myelinolysis**

Demyelination of white matter tracts in the pons may be seen following overly aggressive correction of severe hyponatremia. Although classically this is restricted to the central pons, sparing the periphery, the demyelination
may extend into the midbrain, thalamus, and basal ganglia. Occasionally, only these extrapontine sites are involved; hence, the entity is no longer referred to as central Pontine myelinolysis. Initially, high signal edema is seen. Although some of the abnormality is reversible, progression to frank cavitation also occurs. 29, 69 (Fig. 17,18,19)

Figure 17. T2-weighted MRI scan of the brain demonstrating patchy areas of signal change within the pons that are consistent with demyelination or central pontine myelinolysis

Figure 18. T1-weighted MRI scan of the brain demonstrating patchy areas of signal change within the pons that are consistent with demyelination or central pontine myelinolysis
Figure 19. A post mortem section through the pons showing central pontine myelinolysis.

Figure 20. Posterior reversible leukoencephalopathy in a posttransplant patient receiving cyclosporin and presenting with visual disturbances. Confluent white matter signal abnormalities extend throughout the parietal and occipital white matter. (A, FLAIR; B, FSE T2-weighted; C, SE T1-weighted; D, SE T1-weighted with contrasted).

Figure 21. White matter changes after radiotherapy. Edema and gliosis are seen as hyperintensity on FLAIR (A) and T2-weighted (B) images, and as hypointensity on T1-weighted images postcontrast (C). Note the normal variant venous angioma (C).

Leukodystrophies

Leukodystrophies are dysmyelinating disorders that represent defects in the formation or maintenance of myelin. Whereas most leukodystrophies present in childhood, metachromatic leukodystrophy and adrenomyeloneuropathy...
have an adult onset and may enter into the clinical differential of MS. In the adult variant of metachromatic leukodystrophy, symmetric diffuse involvement of white matter, sparing the subcortical U fibers, is seen. 60

Figure 22. Adrenoleukodystrophy

Lesions in adrenomyeloneuropathy initially involve the pyramidal tracts, usually in the posterior limbs of the internal capsules. With progression of disease, the symmetric posterior parietal white matter involvement of adrenoleukodystrophy may be seen. Female carriers of X-linked adrenoleukodystrophy present with a late-onset neurologic dysfunction, as in adrenomyeloneuropathy. 78

OPTIC NEURITIS AND MS

Acute monosymptomatic optic neuritis (ON) is a common manifestation of MS, and the reported risk for developing MS varies widely. A small, long-term 8-year follow-up study demonstrated that 50% of patients develop clinically definite MS. 11 A larger study of 388 patients by the Optic Neuritis Study Group demonstrated that 30% of patients with ON progress to clinically definite MS within 5 years. 46 The risk of progression to clinically definite MS correlated highly with the number of lesions seen at MR imaging. A normal brain MR image at presentation did not preclude the development of MS in the future, with 16% of patients developing MS. One half (51%) of those with three or more MR imaging lesions went on to develop MS. 46

As with MS plaques in the brain, enhancement may be seen in the optic nerves during the acute phase, resolving over weeks to months (Fig. 23). 86 MR imaging of the brain is used to evaluate for lesions suggestive of MS, which are found at presentation in 57% of patients. 33 Although ON is most often associated with typical MS lesions in the brain, Devic's neuromyelitis optica is a syndrome in which a severe myelopathy is associated with the neuropathy. Brain lesions are absent. It has been regarded as a form of MS or as a separate neurologic syndrome. Recent MR imaging evidence suggests that it may in fact be distinct from MS, because the MT ratio of white matter in these patients is similar to that of a healthy cohort. 16 Another cause of ON, Leber's hereditary optic neuropathy, is a mitochondrial disorder, which in females can manifest in a manner identical to MS. 24

BRAINSTEM SYNDROMES, TRANSVERSE MYELITIS AND MS

Progression to clinically definite MS is seen in nearly half of patients presenting with transverse myelitis (42%) and nearly two thirds of those presenting with a brain stem syndrome. 39, 48

MR IMAGING IN THE DIAGNOSIS OF MS: PREDICTIVE VALUE IN THE CLINICALLY ISOLATED SYNDROME

MS typically presents as an acute, reversible episode of neurologic dysfunction—the clinically isolated syndrome (CIS). Spinal cord, optic nerve, or brain stem involvement accounts for most cases. Poser et al set forth criteria to establish a definitive diagnosis of MS. 56 Clinically definite MS (CDMS) requires clinical evidence of two lesions
separated in time and space. A positive MR image can establish the diagnosis of CDMS in patients who have had two attacks but have clinical evidence of only one lesion. Furthermore, Poser and colleagues defined a category of laboratory-definite MS (LDMS) in patients with oligoclonal bands in the CSF and positive MR imaging findings, but without satisfying the more stringent criteria of clinical evidence.

Figure 23. Optic neuritis in a patient with MS. Sagittal (A) coronal (B) and axial (C) SE T1-weighted images through the optic chiasm demonstrate extensive enhancement of the optic nerves, tracts, and chiasm. Axial FLAIR image shows typical MS plaques.

The Poser criteria reflected the fact that when a patient presents with a CIS, the condition may progress to CDMS, or it may be a solitary event with no subsequent attacks. These criteria recognized that MR imaging and other paraclinical tests have an important role in predicting the development of MS. CSF oligoclonal bands, according to some authors, have a higher positive predictive value than MR imaging; however, recent studies have established the predictive power of MR imaging. O'Riordan et al have shown a strong correlation between the baseline T2-weighted MR image appearance and the probability of progression to CDMS in a 10-year follow-up study. Two thirds of their patient population had lesions at baseline, and 83% of these patients progressed to CDMS at 10 years. Of the one third with normal MR images, only 11% progressed to CDMS. Furthermore, the number of lesions at baseline correlated with the probability of progression to MS and with the disability scores at 5 and 10 years lateral. Specificity may be improved by the presence of an enhancing lesion at the expense of sensitivity, as these lesions are found in approximately one third of patients undergoing MR imaging. A higher incidence of abnormal MR images at initial presentation is found using thin sections (3 mm) and higher field strength (1.5 Tesla).

Attempts to increase the diagnostic accuracy of MR imaging by using fixed criteria have been proposed (Table 1). Initially, these attempts were based solely on CSE, PD, and T2 imaging. The Paty et al, criteria used four or more lesions (Paty A) or three lesions with one bordering a ventricle (Paty B) as strongly suggestive of MS. Fazekas et al, developed criteria similar to Paty for using MR imaging to predict the development of MS. Three or more lesions were required, with two of the following features: found to be larger than 5 mm, and in a periventricular or infratentorial location. These criteria reflect the lesser weight given to lesions in the centrum semiovale, which are commonly found incidentally and with small vessel ischemia. These criteria led to a further improvement in specificity (96%) at the expense of a decrease in sensitivity (81%).

Table 1. MR IMAGING CRITERIA FOR CLINICAL PROGRESSION TO MS

Paty et al, 53, 1988

- 4 lesions
- > 3 lesions, including 1 periventricular lesion
Fazekas et al, 13, 1988

3 lesions with two of the following properties:

- Infratentorial;
- Periventricular
- > 5 mm in diameter

Barkhof et al, 2, 1988

Cumulative model based on 4 lesion properties:

- > 1 juxtacortical
- > 1 enhancing or > 9 nonenhancing
- > 1 infratentorial
- > 3 periventricular

Barkhof et al incorporated contrast enhancement into the scheme for MS criteria. Continuous variables were dichotomized, and logistic regression was used to model the clinical outcome at 2 years. Based on this model, more accurate criteria than those of Paty and Fazekas were achieved. The Barkhof criteria require the presence of at least one enhancing lesion (or nine lesions visible on T2-weighted imaging), one juxtacortical lesion, one infratentorial lesion, and three periventricular lesions. Recently, a prospective study has found the Barkhof criteria to be more accurate than the Paty and Fazekas criteria. The Paty and the Fazekas criteria showed identical results: sensitivity, 86%; specificity, 54%; accuracy, 64%; positive predictive value, 46%; and negative predictive value, 89%. The Barkhof criteria showed the following: sensitivity, 73%; specificity, 73%; accuracy, 73%; positive predictive value, 55%; and negative predictive value, 85%. These values are comparable to those in Barkhof et al's original report.

It is essential to note that these criteria are developed to establish the probability of progression to MS in the context of the CIS. They have not been evaluated in terms of their ability to differentiate MS from other differential diagnoses. Whether improvements in these criteria may be made by including further imaging characteristics or novel imaging sequences (e.g., magnetization transfer) remains to be seen. One could imagine using Barkhof's regression model on a case by case basis to give a probability for an individual patient to progress to MS based on a baseline MR image, and, as more criteria are met, the higher will be the likelihood for progression. This may be more valuable to an individual patient than a fixed set of criteria.

SUMMARY

MR imaging plays a key and significant role in the assessment of patients with MS. Because of its high sensitivity, MR imaging of the brain is the single most useful investigation during the diagnostic work-up of the patient with clinically isolated syndrome. Knowledge of the characteristics of MS lesions, anatomic distribution of lesions, differential diagnosis, and most important, the clinical context, markedly improve the specificity of the MR imaging examination. It is clear that findings on MR imaging can be used to predict future conversion to clinically definite
MS before a second clinical exacerbation occurs. The data suggest a valuable role for counseling individual patients at presentation, possibly selecting patients for clinical trials aimed at delaying disease progression. Potential MR imaging markers of inflammation, demyelination, and axonal loss are helping to further our understanding of the disease process and the resulting clinical disability. The use of serial MR imaging studies to monitor therapy in individual patients will depend on the ability in the future to better understand the relationship between disease activity detected in the short term by MR imaging and long-term disability or response to therapy.

- **Addendum**
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**REFERENCES**

**References**


