Magnetic resonance imaging in multiple sclerosis

Magnetic resonance imaging (MRI) has become the primary technique with which neurologists support the diagnosis of multiple sclerosis (MS), and with which researchers monitor disease evolution in both natural history studies and treatment trials. This review summarises the contribution of brain and spinal cord MRI to the diagnosis of MS, illustrating the appearance of MS pathology on the most common MRI sequences. We also discuss the differences in MRI findings between the clinical types of MS and the development of newer non-conventional sequences.

Beside the ability to detect the dissemination of lesions in space, serial MR scanning can also confirm the dissemination of lesions in time

THE CONTRIBUTION OF MRI TO THE DIAGNOSIS OF MS

The first application of MRI in MS was described in 1981. Since then, MRI of MS has rapidly evolved and new acquisition techniques, characterised by increased sensitivity and specificity with respect to pathology, have been developed. MRI is now an important paraclinical tool for the diagnosis of MS because it allows detection of MS lesions *in vivo* throughout the central nervous system. Beside the ability to detect the dissemination of lesions **in space**, serial MR scanning can also confirm the dissemination of lesions **in time**. Nevertheless, the signal abnormalities of MS lesions alone are not sufficient for a diagnosis of MS because similar patterns of abnormalities can be detected in other neurological diseases and even in normal people. However, taking into account different radiological findings, including lesion number, location, size, and enhancement, brain and spinal cord MRI findings can often support the clinical diagnosis of MS with a high degree of confidence.
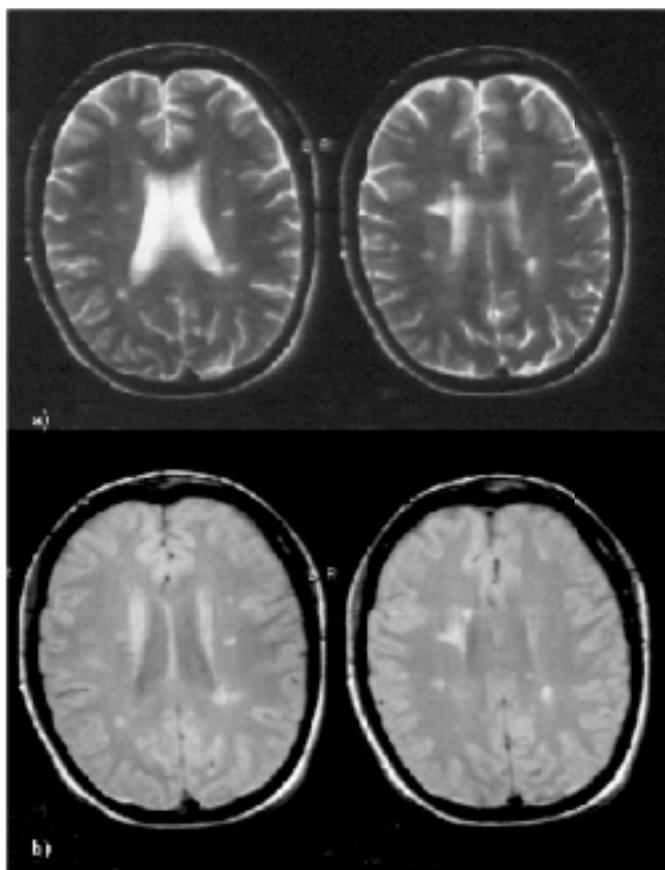
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CONVENTIONAL MR BRAIN IMAGING

T2-weighted imaging

The conventional spin echo (CSE) T2-weighted sequences are widely applied in MS. They are characterised by long repetition time (TR) and long echo time (TE). When a short TE is applied instead, the sequences are referred to as proton density (PD)-weighted images. The T2- and PD-weighted images are very robust and easy to apply across centres. Moreover, these images are the most sensitive for detecting MS lesions. Both acute and chronic lesions appear on T2 and PD-weighted images as areas of high signal intensity compared with the adjacent normal regions (Fig. 1). Discrete MS lesions are relatively well circumscribed, but may show a halo of less striking hyperintensity, probably due to oedema in the very acute stage of inflammation. MS plaques are usually round or ovoid in shape, with the main axis perpendicular to the principal axis of the lateral ventricles and parallel to the white matter vessels (perivenular). They commonly range from a few mm to more than 1 cm in diameter. Rarely, lesions can be very large, with a pseudo-tumour appearance. Some lesions are confluent and may have an irregular shape. As a consequence, periventricular signal changes may take on a scalloped appearance.

MS lesions have a high propensity for certain regions of the brain. Characteristic areas of involvement are the periventricular white matter and the corpus callosum. The involvement of the corpus callosum is easily visualised in the sagittal plane where, beside the focal lesions, a degree of atrophy can also be detected (Fig. 2). Lesions are often localised in the brainstem, mainly in the floor of the fourth ventricle, periacqueductal region, mesencephalon (Fig. 3), pons, and cerebellar peduncles. Lesions frequently appear at the interface between grey and white matter (i.e. cortical-subcortical regions) and sometimes in the basal ganglia. Discrete hyperintensities adjacent to the body or temporal horn of the lateral ventricles are frequent in MS and are rarely seen in other disorders. Lesions around the frontal or posterior horns are also often detected (Fig. 1), but are more difficult to distinguish from the periventricular caps that can occur in normal people. Although pathological examinations of MS brains report a high number of cortical lesions, such lesions are rarely visualised on MR because of the small size of these abnormalities, less optimal contrast of MS lesions against adjacent grey matter, and partial volume effects from adjacent CSF.

Although the CSE T2-weighted sequence is the most sensitive paraclinical test in the diagnosis of MS, its specificity is limited. Any pathology from oedema and mild demyelination through to destructive lesions with axonal loss may appear bright, and there is evidence than even remyelinated lesions have abnormal signal. This lack of histopathological specificity accounts in part for the modest correlation between clinical disability and MRI parameters, which is known as the clinical-radiological paradox in MS.

Other disadvantages of CSE T2/PD-weighted scans are the relatively long acquisition time and the lack of sensitivity in detecting lesions adjacent to CSF. To overcome the former limitation, faster sequences called fast spin echo (FSE), which are generally equivalent to CSE in their ability to detect hyperintense lesions and require only a few minutes to cover the whole brain, have been developed. Fluid-attenuated
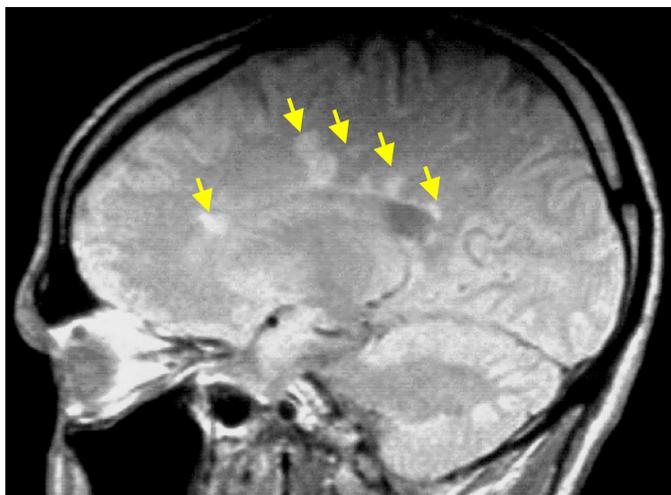

Figure 1 MS lesions are evident on T2-weighted images (a) and on proton density (PD)-weighted fast spin echo (FSE) images (b). They appear as areas of increased signal intensity compared with the adjacent regions, localised around the lateral ventricles and within the white-matter of the brain.

Figure 2 Multiple lesions in the corpus callosum (see arrows) on a sagittal PD-weighted fast spin echo (FSE) image.
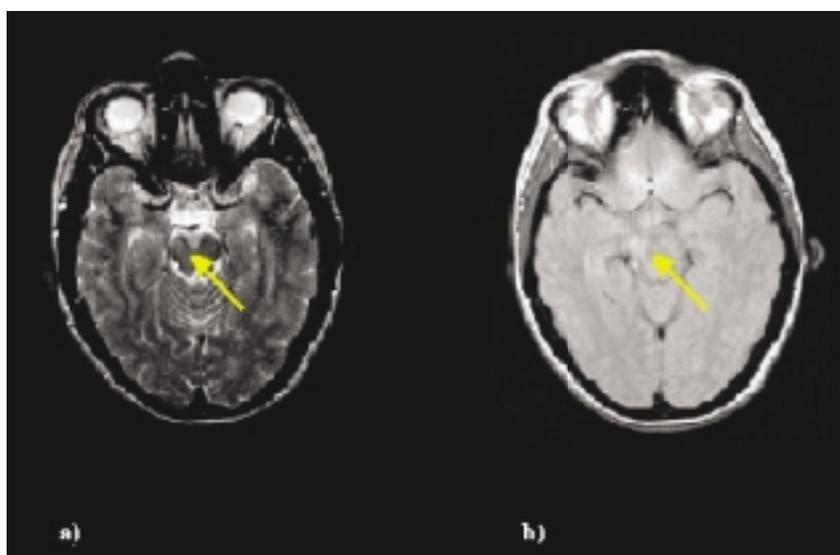

Figure 3 MS lesion in the right cerebral peduncle on (a) T2-weighted (see arrow) and (b) PD-weighted (see arrow) fast spin echo (FSE) images.

inversion recovery (FLAIR) images, that are heavily T2-weighted images in which the high signal from CSF is suppressed, allow instead a better visualisation of both cortical–subcortical and periventricular lesions. Therefore, newer fast-FLAIR sequences combining the advantages of both FSE and FLAIR are often used in conjunction with conventional spin echo for imaging in MS (Fig. 4).

Gadolinium-enhanced imaging

Gadolinium-diethyl-enetriaminepentacetic acid (Gd-DTPA) is a paramagnetic intravenous contrast agent that is used to increase the diagnostic specificity of MRI in MS. It reaches brain regions where there is damage to the blood–brain barrier, which is an early pathological event in the development of MS lesions. The paramagnetic effect induces shortening of the T1 relaxation time of nearby water protons, and thus these regions are visualised as areas of enhancement on postcontrast T1-weighted images. Gadolinium enhancement is a regular finding in new inflammatory MS lesions, but may also indicate the recurrence of inflammation within pre-existing lesions. The enhancement is a transient phenomenon and, in over 70% of new lesions it lasts 1 month or less. Approximately 30% of lesions continue to enhance for more than a month, and a smaller number (5%) persist for 3–4 months. Lesions demonstrating enhancement for more than 4 months are more suggestive of other inflammatory, infectious or neoplastic diseases. Steroid treatment of acute attacks shortens the period of enhancement. The presence on the same images of acute enhancing lesions and old non-enhancing lesions is suggestive of dissemination of lesions **in time** (Fig. 5).
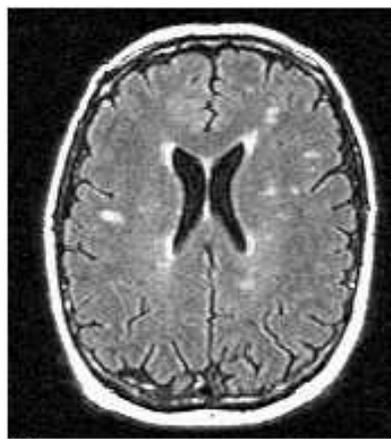
Figure 4 MS lesions are evident in the periventricular regions, in the white-matter, and in the cortical/subcortical areas on (a) PD-weighted fast spin echo (FSE) image and (b) three-dimensional fast-FLAIR image, but they are more evident on the fast-FLAIR scan.

Figure 5 Active MS lesions are seen as areas of enhancement on post-contrast (a) T1-weighted images (yellow arrows). Old non-enhancing lesions on the same postcontrast T1 image appear as areas of hypointensity ('black holes') compared with adjacent regions (red arrows). Note that most of the T2 hyperintensities detected on (b) T2-weighted scan appear isointense on T1-weighted images. These postcontrast T1 images were acquired 5 min after an injection of a triple dose of gadolinium (0.3 mmol/kg).
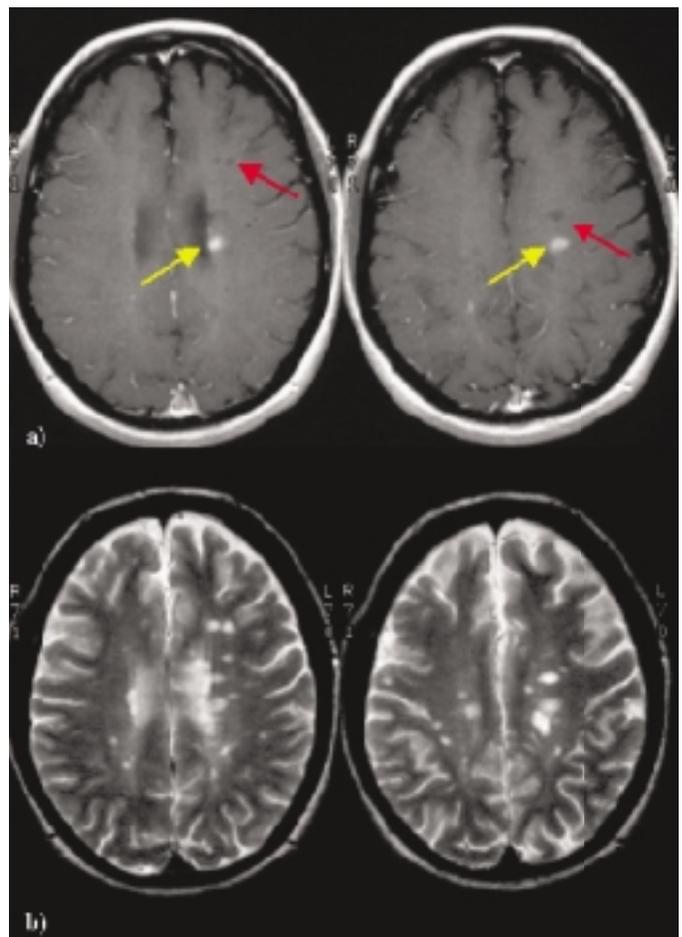
The enhancement seen in MS lesions may appear in different shapes:
- global and uniform, especially in new enhancing lesions;
- partial and irregular, mainly in reactivated lesions;
- 'ring', when the new inflammatory demyelinating process occurs at the expanding edge of a lesion.

The number of enhancing lesions that can be detected depends both on the concentration of the gadolinium and on the timing of

the scan. A dosage of 0.1 mmol/kg body weight and a time interval of 5 min between the injection of gadolinium and the post-contrast T1-weighted scan is sufficient for diagnostic purposes. However, triple-dose contrast (0.3 mmol/kg) increases the number of enhancing lesions detected, presumably because it identifies a 'lower-grade' of inflammation. Triple-dose MRI is therefore significantly more sensitive than single-dose for monitoring MS disease activity. The occurrence of active lesions is related to the short-term clinical course, e.g. relapse rate; their relationship with long-term disability is less clear.

In conclusion, gadolinium enhancement has become a valuable MRI technique to monitor the evolution of the disease, either natural or modified by treatment.

Unenhanced T1-weighted imaging

On conventional T1-weighted sequences, which use short TR and short TE, around 10–30% of T2 hyperintensities appear as areas of low signal intensity compared with normal white matter, while the remaining lesions appear isointense (Fig. 5). In the acute phase, i.e. when the lesion shows enhancement on a post-contrast T1-weighted scan, T1 hypointensity is probably a consequence of marked oedema with or without matrix destruction. This acute T1 hypointensity can disappear after 1–6 months, due to the resorption of oedema and inflammatory cells and possibly remyelination. Chronic foci of hypointensity, also known as persisting 'black holes', indicate instead areas with the most severe tissue damage. Several histopathological studies have found a correlation between the degree of T1 hypointensity of lesions and axonal loss. These hypointense T1 lesions correlate better with disability than do lesions on T2 images, and therefore the T1 lesion load may be more suitable for monitoring disease progression than the overall T2 lesion load.

It is not clear what factors contribute to the development of particularly destructive MS lesions. They occur more often in secondary progressive MS. Brain atrophy, a consequence of extensive structural damage, is present even in the early stage of MS, becomes more prominent with increasing disease duration and disability, and can also be assessed on T1-weighted images using a variety of semi-automated software.

Differential diagnosis

Several disorders cause MRI signal abnormalities similar to those of MS. The following should be considered in the radiological differential diagnosis.

Ageing

Multifocal areas of high signal intensity within the cerebral white matter, with or without involvement of the periventricular regions, are frequently seen on T2-weighted images with normal ageing. These are associated pathologically with arteriosclerotic changes in small vessels. The frequency of such lesions increases with age and with the presence of vascular risk factors, such as hypertension and diabetes. They may also occur in people with a history of migraine. These hyperintensities are located throughout the deep and subcortical white matter, usually sparing the corpus callosum and infratentorial areas. High signal intensities around the frontal horns (caps) are a normal finding, and they are also sometimes seen in the occipital lobes.

Cerebrovascular disease

Diffuse periventricular changes and small deep infarcts are seen in patients with subcortical arteriosclerotic encephalopahy (Binswanger's disease). However, the lesions surrounding the ventricles tend to be smoother than in MS, and spare the subcortical U-fibres. Multiple deep infarcts due to intracranial small vessel disease appear as 'lacunar' lesions and involve the deep white matter, basal ganglia and central pons.

Vasculitis

Vasculitis and immune-mediated vasculopathies are important to consider in the differential diagnosis of MS. Systemic lupus erythematosus and the antiphospholipid syndrome can both cause white matter hyperintensities in the deep and mainly subcortical regions. Gd-enhancement of these lesions is probably less common than in MS. Behcet's disease involves primarily the brainstem and diencephalon.

Infectious and inflammatory diseases

Acute disseminated encephalomyelitis (ADEM) can cause signal abnormalities identical to those of MS. However, using both a post-enhanced scan and a T2-weighted scan after a sufficient follow-up interval, it is possible to minimise the risk of misdiagnosis. Because ADEM is a monophasic illness, all, or at least most, lesions enhance in the acute phase, while none does so in the chronic phase. Moreover, in ADEM pre-existing lesions often disappear and new lesions

do not occur at follow-up. Neurosarcoidosis can cause multiple enhancing lesions throughout the central nervous system (CNS), associated with diffuse meningeal enhancement (Fig. 6). Progressive multifocal leukoencephalopathy can cause large and multifocal abnormalities in the subcortical white matter without mass effect or contrast enhancement, while HIV encephalitis and subacute sclerosing panencephalitis can cause diffuse and focal white matter lesions.

Leukodystrophies and toxic metabolic diseases

These disorders are characterized by different types of demyelination or dismyelination in the CNS caused by congenital metabolic errors, and by toxins such as radiation therapy. In most of these conditions, the lesions are diffuse, symmetrical and confluent in the periventricular and subcortical white matter. Mitochon-

Figure 6 A case of neurosarcoidosis: multiple lesions are localised in the periventricular regions and in the white-matter on (a and b) T2-weighted conventional spin echo (CSE) images (see arrows). Frontal meningeal enhancement is evident on (c and d) Gd-enhanced images (see arrows).


drial encephalopathy can show discrete lesions, which have a predilection for the occipital lobes and look somewhat like ischaemic strokes.

Malignancies
Brain tumours can cause both multiple hyperintensities or solitary areas of signal abnormality, often with mass effect. Rarely, MS lesions produce such a tumour-like appearance.

Diagnostic criteria for MS
The differences in lesions distribution, shape and size between MS and other CNS disorders have stimulated the development of MRI criteria to help in the diagnosis of MS. The existing diagnostic criteria were recently reassessed and modified by an international panel in order to create new criteria that could be used by the practising physician, and in clinical trials (Table 1). Traditional diagnostic criteria require clinical evidence of dissemination **in time** and **space**, i.e. at least two relapses in separate locations. When the clinical evidence alone does not allow a diagnosis to be made, the new criteria use radiological and laboratory findings, including MRI, analysis of cerebrospinal fluid (CSF) and visual evoked potentials (VEP), to make the diagnosis. Among these paraclinical tests, MRI is the most sensitive and specific tool for demonstrating dissemination **in time** and **space**.

An MR scan is considered to show dissemination **in space** when there is evidence of at least three of the following:
- one gadolinium-enhancing lesion or nine T2 hyperintense lesions if a Gd-enhancing lesion is not present;
- at least one infratentorial lesion;
- at least one juxtacortical lesion (i.e. involving the subcortical U-fibers);
- at least three periventricular lesions.

These criteria are of proven value in predicting those patients who will develop clinically definite MS after an isolated neurological episode.

MRI can provide evidence of dissemination **in time** when:
- a Gd-enhancing lesion is demonstrated on a scan taken at least 3 months following onset of single clinical attack at a site different from the attack, or
- in the absence of Gd-enhancing lesions on the 3 month scan, a subsequent follow-up scan shows a Gd-enhancing or a new T2 lesion.

As a minimum, at least one clinical episode typical of MS must have occurred, and MRI evidence
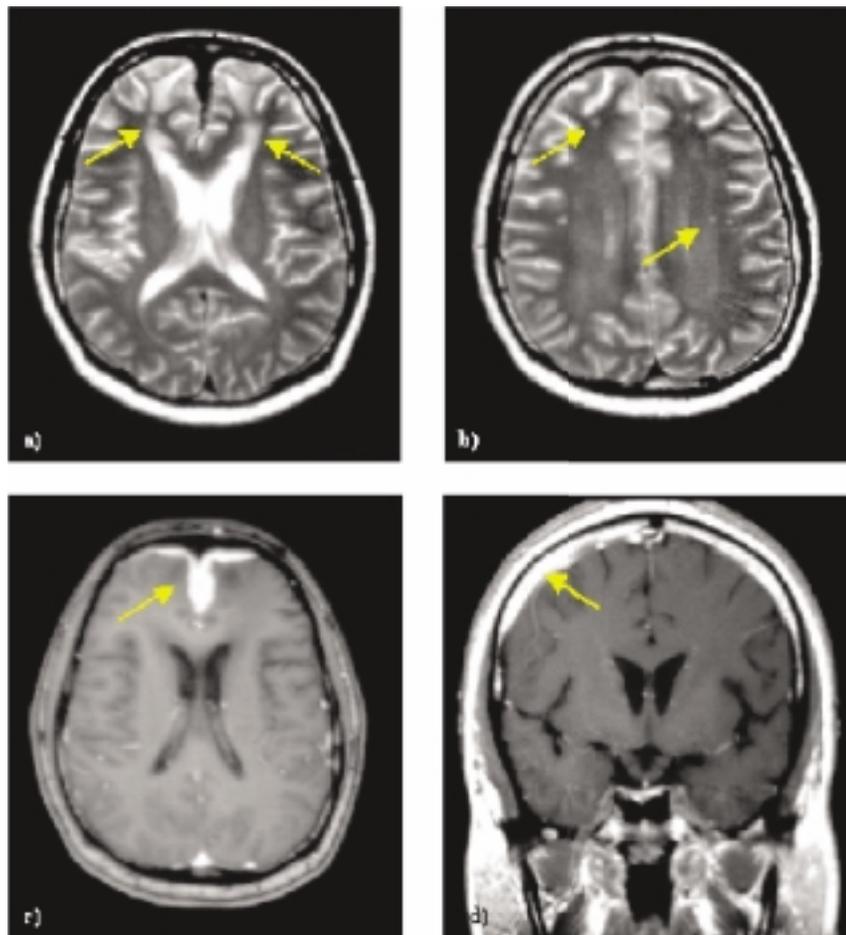
Table 1 Diagnostic criteria for MS (From McDonald et al. Ann Neurol 2001; 50 : 121–127)

Clinical presentation	Additional data needed for MS diagnosis
Two or more attacks; objective clinical evidence of two or more lesions	None
Two or more attacks; objective clinical evidence of one lesion	Dissemination **in space,** demonstrated by MRI *or* two or more MRI lesions consistent with MS and positive CSF *or* further clinical attack involving different site
One attack; objective clinical evidence of two or more lesions	Dissemination **in time,** demonstrated by MRI *or* second clinical attack
One attack; objective clinical evidence of one lesion (clinically isolated syndrome)	Dissemination **in space,** demonstrated by MRI *or* two or more MRI lesions consistent with MS and positive CSF; and dissemination **in time,** demonstrated by MRI *or* second clinical attack
Progression from onset suggestive of MS	Positive CSF and dissemination **in space,** by MRI evidence of nine or more T2 lesions *or* two or more cord lesions *or* 4–8 brain and one cord lesion *or* positive VEP with 4–8 MRI lesions or positive VEP with less than four brain lesions plus one cord lesion; and dissemination **in time** by MRI *or* continued progression for one year

VEP, visual evoked potential.

for a separate new lesion at least 3 months later is required. If the criteria indicated are fulfilled, the diagnosis is MS; if they are partially met, the diagnosis is 'possible MS'.

SPINAL CORD IMAGING

The spinal cord is a common site of involvement in MS. In some cases, especially primary progressive patients, the spinal cord may be the only site to be involved, and in patients with clinically-isolated syndromes it may be the first region of the CNS to be affected. A postmortem study in patients with MS revealed spinal cord involvement in 99% of cases. An MRI study using multi-array coils and FSE images showed that lesions in the spinal cord could be seen in 75% of cases. MS cord lesions are more difficult to detect than in the brain because they are less conspicuous and spinal MRI is technically more challenging.

Spinal cord lesions in MS have a similar signal pattern as cerebral lesions, except for the absence of 'black holes'. Their characteristics and distribution are well known, as is their absence in healthy elderly people. On sagittal scans, they have a cigar shape and may be located centrally, anteriorly, or posteriorly (Fig. 7). Axial scans show their extension toward the periphery with a propensity for the dorsal columns. Spinal MS lesions commonly occupy only part of the cross-sectional area of the cord and they rarely exceed two vertebral segments in length. The cervical spinal cord is twice as likely to be affected than the lower cord, and the mid-cervical region is most often involved. Acute spinal cord lesions may show swelling and enhancement. Disease activity, i.e. contrast enhancement and the development of new lesions,


Figure 7 An MS lesion at C3-C4 level (arrow) on a longitudinal T2-weighted fast spin echo (FSE) spinal cord image.

Figure 8 Spinal cord angioma: sagittal T2-weighted MRI reveals serpiginous flow voids, representing the dilated draining veins, on the dorsal and ventral surface of the lumbar cord, and high signal within the cord (From Miller DH, Kesselring J, McDonald WI, Paty DW, Thompson AJ (1997) Magnetic Resonance in Multiple Sclerosis. Cambridge University Press).
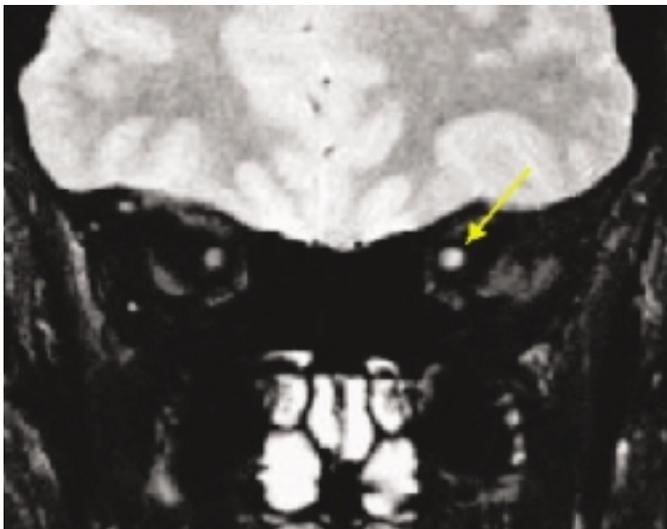
is much less frequent in the cord than in the brain. However, new cord lesions are more likely to be symptomatic than new brain lesions. Diffuse signal hyperintensity in the spinal cord is also seen in primary progressive MS.

The quality of spinal cord imaging is important for diagnosis and research into MS. Surface coils help to increase the spatial resolution, whilst phased array coils are particularly useful in providing images of the whole spinal cord without moving the patient. The optimum sequence for detecting MS lesions in the spinal cord is still debated. Because the CSE sequences are characterized by a long acquisition time, FSE images, which can provide reasonable resolution and image quality with an acceptable acquisition time, are preferred. Axial images may help to confirm an equivocal lesion seen on a sagittal scan.

Intrinsic cord lesions do not develop with ageing *per se*, but may occur in vasculitis, immune-mediated vasculopathies, infectious and other inflammatory diseases, and tumours. Spinal cord arteriovenous malformations can be reliably detected using high magnetic fields (1.5 Tesla scanner) with FSE and contrast-enhanced scanning (Fig. 8).

OPTIC NERVE IMAGING

Optic neuritis is a frequent manifestation of MS. In about 25% of the cases it is the presenting symptom. Lesions most often involve the intraorbital portion of the nerve; the intracanalicular portion of the nerve is affected with moderate frequency, while lesions of the intracranial portion of the nerve and chiasm are seen less often. MRI of optic nerve is challenging, because of its tortuosity and mobility, its short length, and the surrounding CSF and orbital fat. Best results are obtained with multiarray surface coils, high-resolution sequences and coronal slices with fat suppression methods. Such approaches reveal the lesions of optic neuritis in more than 90% of patients. High quality optic nerve imaging is important in the diagnostic work-up of patients with unexplained optic neuropathy but is not required in a classical case of optic neuritis (Fig. 9).

Figure 9 A patient with acute optic neuritis shows a lesion (arrow) in the intraorbital portion of the left optic nerve on a PD-weighted fat saturated fast spin echo (FSE) image.

MRI FINDINGS IN DIFFERENT CLINICAL TYPES OF MS

The MRI findings, and activity, of the brain and spinal cord are different in the different clinical types of MS. Patients with relapsing–remitting and secondary progressive MS have higher MRI activity (on average 20 active lesions per year),

whereas patients with primary progressive and benign disease have lower MRI activity (three active lesions per year and nine active lesions per year, respectively). Recent MRI studies have shown that relapsing–remitting patients develop slightly more active lesions than patients with secondary progressive MS. Considering the brain disease burden commonly calculated on T2-weighted images, the lesion load is significantly higher in patients with secondary progressive MS than in relapsing–remitting patients and it is also significantly higher in secondary progressive patients than in primary progressive patients matched for disease duration. A cross-sectional study found that patients with benign MS and a mean disease duration of 15 years had the same lesion load as patients with relapsing-remitting MS with 4.4 years of disease duration. In patients with secondary progressive MS, a larger number of lesions are located in the infratentorial regions and they tend to be confluent in the periventricular areas. Moreover, secondary progressive patients have a larger number of hypointense lesions compared with patients with relapsing–remitting and primary progessive MS, and they have more cerebral and spinal cord atrophy. Although the number of focal T2 lesions in the cord does not significantly differ between MS clinical types, diffuse spinal cord signal abnormalities are found in primary progressive and, to a lesser degree, in secondary progressive MS.

NEW MRI TECHNIQUES: MAGNETIZATION TRANSFER IMAGING, SPECTROSCOPY AND DIFFUSION

New MR techniques have been developed to provide additional information on the pathological substrates of MS lesions. They offer insights into the pathophysiology of the disease. Magnetization transfer imaging (MTI), proton magnetic resonance spectroscopy (^{1}H-MRS) and diffusion-weighted imaging give information about the severity of tissue damage within and beyond MS lesions, i.e. in the normal-appearing white matter.

In contrast to conventional MRI techniques, which acquire their signal from the free water protons, magnetization transfer (MT) contrast is based on saturation of the macromolecular protons and the subsequent exchange of magnetization into the free proton pool. The MT ratio (MTR) provides an index of macromolecular integrity, because high MTR values are reported in myelinated white matter. Using MTI, decreased MTR values have been found

in severe demyelination and axonal loss, in comparison with slightly decreased values in oedema and mild demyelination. Reduced MTR values have also been noticed in the normal-appearing white matter. Subtle MTR changes in the normal-appearing white matter may precede the appearance of MS lesions. Histopathological studies have recently shown that the MTR values correlate with the proportion of residual axons and the demyelinating activity within lesions.

^{1}H-MRS provides an *in vivo* method for measuring tissue metabolites. They include:

- N-acetyl aspartate (NAA), which is present in high concentration in neurones;
- choline-containing compounds (Cho), which is a constituent of cell membranes;
- creatine plus phosphocreatine (Cr), which are present in astrocytes and oligodendrocytes and to a minor extent in neurones;
- lactate, which is a marker of the presence of macrophages;
- myo-inositol, a possible glial cell marker.

Therefore, an altered level of each metabolite may reflect the different histopathological processes that occur in MS. For example, a decreased level of NAA reflects axonal loss or dysfunction, increased Cr level may reflect gliosis, and increased Cho reflects increased membrane turnover or cellularity. MRS studies have shown in acute MS lesions, a reduction of NAA and an increase of both Cho and lactate (Fig. 10). Chronic lesions are characterised by reduced NAA and reduced Cho level. Spectros-

Figure 10 On the left is a structural brain image overlaid with a grid of ^{1}H-MRS voxels. The top right spectrum corresponds with the highlighted voxel to the left of the brain image, and comes from normal-appearing white matter. The bottom right spectrum corresponds with the highlighted voxel to the right of the brain image, and comes from a lesion containing voxel. The N-acetyl-aspartate peak (at c. 2 p.p.m) appears reduced in amplitude in the lesion containing voxel when compared with the normal-appearing white matter voxel.
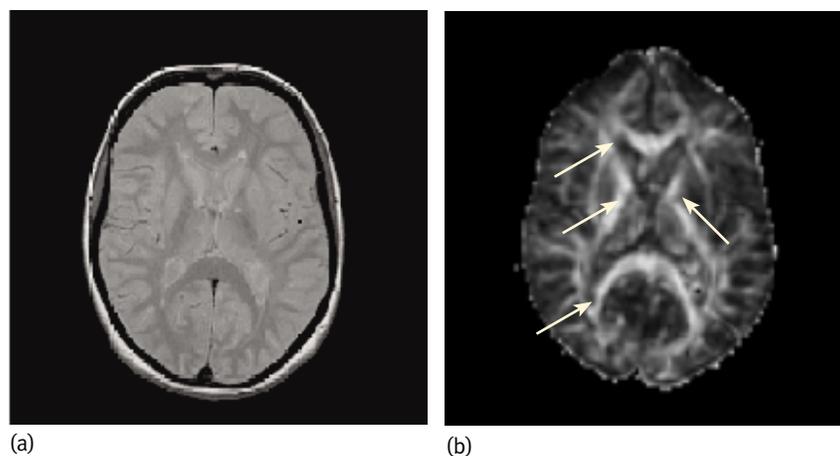
(a)　　　　　　　　　　　　　　　(b)
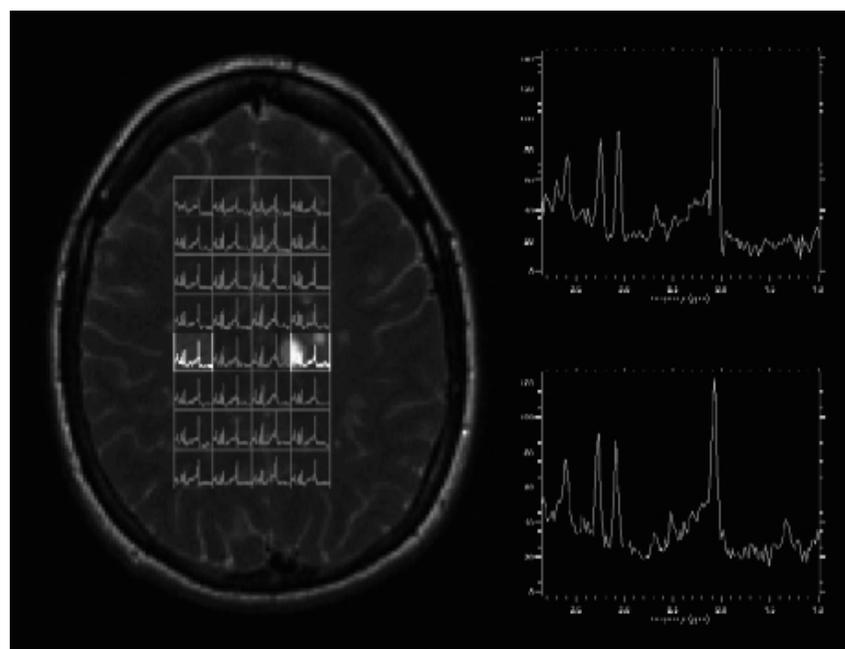
Figure 11 MS lesions present on (a) a proton density image are evident on (b) a fractional anisotropy map (arrows). On the factional anisotropy map the brightest regions represent areas of high anisotropy, characterized by aligned white fibre tracts, and MS lesions appear as areas of reduced anisotropy within them.

copy changes in the normal-appearing white matter beyond the focal lesions, including reduced NAA, suggest widespread axonal loss or dysfunction.

Diffusion-weighted imaging is sensitive *in vivo* to the diffusion of water molecules within the brain. In the white matter, water molecules diffuse preferentially parallel to axons, being restricted in the perpendicular direction. This property, termed 'diffusion anisotropy', may be quantified by diffusion tensor imaging (DTI). Diffusion studies show higher amounts of diffusion (diffusivity) and lower anisotropy in MS lesions than in the adjacent regions (Fig. 11); the same pattern is present in the normal appearing white matter of MS patients compared with the white matter of normal controls. Anisotropy maps derived from DTI reveal white matter tracts and the effect of lesions upon them, in a unique manner. Methods have been recently developed to depict white matter tracts fibres, and future studies will investigate the relationship between connection fibres and functional activity within the brain.

ACKNOWLEDGEMENTS

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