

**M**ultiple sclerosis (MS) is a common central nervous system (CNS) disease characterised pathologically by the development of multifocal inflammatory demyelinating white matter lesions. Magnetic resonance imaging (MRI) is the gold standard imaging technique for the identification of demyelinating lesions which can be used to support a clinical diagnosis of MS, and MS can now be diagnosed in some patients after a clinically isolated syndrome (CIS) using new MRI diagnostic criteria. Clinical trials of disease modifying treatments include MRI outcome measures of disease activity. The use of MR techniques to study the evolution of MS pathology in vivo is an important tool for obtaining better insights into pathophysiological mechanisms underlying the clinical course. This article will concentrate on the practical application of MRI in the management of MS.

## MRI CONTRAST HELPS TO IDENTIFY MS PATHOLOGY

MR images are said to have contrast if there are differing areas of signal intensity. The contrast can be controlled to a certain extent by the parameters used and can produce images which contain differing levels of contrast depending on tissue content. For example, fat and water produce different image contrast. Images can be weighted towards particular contrast mechanisms. In T1 weighted images, fat is bright and cerebrospinal fluid (CSF) is dark; with T2 weighting, fat is dark and CSF is bright. Proton density (PD) weighting produces image contrast on the basis of the PD of the tissue. Such weighting of images has been exploited to identify inflammatory demyelinating lesions at different stages in their evolution.<sup>1</sup>

### T2 and PD weighted imaging

T2 weighted imaging identifies MS lesions as high signal foci against the low signal background of white matter. However, periventricular lesions are often indistinguishable from the adjacent CSF which is also of high signal with T2 weighting. Contrast from the lesion can be improved here by using PD weighting because of the lower CSF signal with this sequence. Fortunately, T2 and PD weighted images can be acquired together in a single spin-echo sequence providing complimentary information (fig 1).

### Fluid attenuated inversion recovery (FLAIR) sequence

The problem of identifying lesions in the periventricular region, which is a common site for MS lesions, can also be addressed by suppressing the signal from CSF yet maintaining heavy T2 weighting using a fluid attenuated inversion recovery (FLAIR) sequence (fig 1). This sequence is also superior at detecting cortical/juxtacortical lesions. FLAIR is therefore a commonly used MR sequence on clinical scanners when MS has been raised as a possible clinical diagnosis. The only drawback is inferior quality lesion detection in the posterior fossa and spinal cord where PD and T2 weighting are preferred.

### T1 weighted imaging without contrast

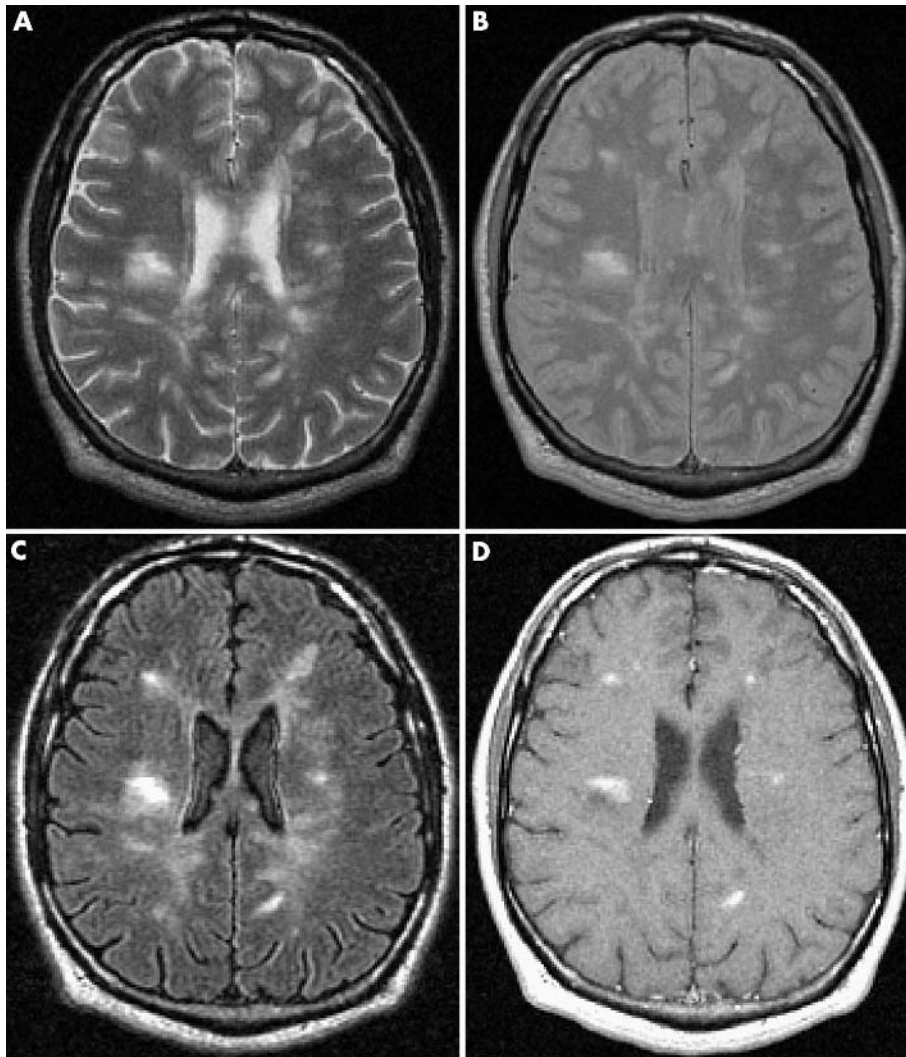
Some high signal lesions on T2 weighted imaging will also be visible on T1 weighted images as areas of low signal compared to the normal white matter and are commonly known as “black holes” (fig 2). Such lesions when newly formed will either disappear with time, when it is thought they are caused by reversible oedema or demyelination, or persist as chronic black holes, when it is thought they are caused by permanent axonal loss.

### T1 weighted imaging with gadolinium enhancement

A gadolinium chelate administered intravenously five minutes before T1 weighted imaging detects blood–brain barrier breakdown in association with active inflammation. New lesions appear enhanced (fig 1) and usually persist for a month on average, making them a useful marker for monitoring disease activity. Such lesions play an important role in indicating dissemination in time within the new diagnostic criteria. Triple dose gadolinium or combination with

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**Figure 1** Axial magnetic resonance imaging (MRI) of a 30 year old man with relapsing remitting multiple sclerosis (MS) showing multiple periventricular lesions: (A) T2 weighted image; (B) proton density (PD) weighted image; (C) fluid attenuated inversion recovery (FLAIR) image; (D) T1 weighted image following administration of gadolinium (Gd) demonstrating enhancing lesions.

magnetisation transfer imaging (see next section) can both increase active lesion detection further but are not required in clinical practice.

### NON-CONVENTIONAL MRI IN MS

The conventional MR techniques already discussed are restricted to the PD, T1, and T2 signal contrast behaviour of MS lesions. While these have transformed the diagnosis of MS and provided information about the significance of lesions, not all the pathological features of lesions can be studied using PD, T2, and T1 weighting, and CNS tissue that appears normal with such images can show pathological changes using quantitative MR techniques that are now discussed.<sup>2, 3</sup>

### Magnetisation transfer imaging (MTI)

Tissues contain protons in the liquid phase (mobile pool) and protons which are bound to macromolecules including proteins and lipids (bound pool). The latter have a very broad magnetic resonance frequency that normally decays too quickly for the scanner to detect. Bound pool protons are constantly in a state of exchange with the mobile pool. If a strong radiofrequency pulse is applied far enough away from the resonance of the mobile pool but is still able to excite the

bound pool, some of the magnetisation is transferred from the bound to the mobile pool. This produces a magnetisation transfer (MT) weighted image and the magnetisation transfer ratio (MTR) can be calculated from the MT image and an image without MT weighting. Magnetisation transfer imaging (MTI) has been shown to be a sensitive marker of pathological change in many neurological disorders and, as a general rule, MTR decreases with increasing pathological change. Correlative MTI-pathological studies have suggested that the myelin content and the axonal count are the most relevant substrates of MTR changes in patients with MS, especially the former.

MTI in MS has focused on three main areas: (1) using MTI with gadolinium to improve lesion detection (discussed earlier); (2) distinguishing lesions of differing severity; (3) studying MTR in brain tissues that appear normal on conventional MRI. In vivo studies have shown that T1-hypointense lesions (“black holes”) have a lower MTR than T1 isointense lesions, supporting the idea that these lesions occur as a result of destructive pathology. MTR values fall considerably when gadolinium enhancement occurs in lesions, with a recovery of MTR over the following months, although not usually back to normal. In some studies, brain MTR declines for several years. The severity of tissue damage

has some correlation with the course of MS, as secondary progressive patients display lower lesion MTR than patients with benign MS. Whole brain MTR and segmented normal appearing white matter MTR are lower in patients than in healthy subjects, and independently predict subsequent disability.

MTI can be used to study the time course of lesion development and has shown that some lesions develop in previously normal appearing tissue in which there is declining MTR up to two years before gadolinium enhancement appears. Such lesions are less likely to recover MTR values compared to lesions developing in tissue with a previously normal MTR. Given the sensitivity of MTI to detect pathological change, guidelines for its use in future clinical trials have been developed.

### Diffusion weighted imaging (DWI)

Diffusion is the random motion of molecules in any fluid system including biological tissue. Diffusion weighted imaging (DWI) refers to the process of making MRI sensitive to the molecular motion of water molecules and is potentially a useful technique for studying white matter structure and pathology. Water diffusion can occur in any direction but occurs preferentially along the orientation of axons because their cell membranes act as barriers to diffusion. Such diffusion is said to be anisotropic and is dependent on the structural integrity of white matter tracts. Any disruption to white matter tracts or axonal membrane permeability should lead to an increase in the apparent diffusion coefficient (ADC) and mean diffusivity (MD), a measure of average molecular motion, and also to a decrease in fractional anisotropy (FA), a measure of the directional preponderance of diffusion which can be obtained with diffusion tensor imaging (DTI).

DWI has been applied qualitatively in clinical practice where it can be used to detect ischaemic changes within 30–90 minutes of acute stroke. DWI and DTI have supplemented conventional MRI techniques for the quantitative study of MS pathology in vivo. DTI studies in MS have shown increased ADC and MD with decreased FA in chronic T<sub>1</sub> hypointense lesions compared to T<sub>1</sub> isointense lesions which is compatible with evidence that T<sub>1</sub> hypointense lesions

### Abbreviations

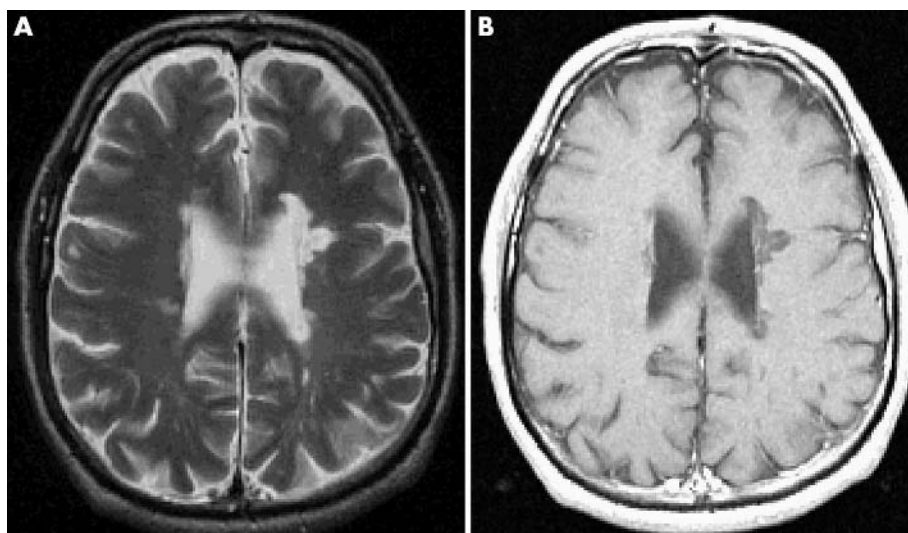
- ▶ **ADC:** apparent diffusion coefficient
- ▶ **ADEM:** acute disseminated encephalomyelitis
- ▶ **CADASIL:** cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy
- ▶ **CIS:** clinically isolated syndrome
- ▶ **CNS:** central nervous system
- ▶ **CSF:** cerebrospinal fluid
- ▶ **DTI:** diffusion tensor imaging
- ▶ **DWI:** diffusion weighted imaging
- ▶ **EDSS:** expanded disability status scale
- ▶ **FA:** fractional anisotropy
- ▶ **FLAIR:** fluid attenuated inversion recovery
- ▶ **MD:** mean diffusivity
- ▶ **MRI:** magnetic resonance imaging
- ▶ **MRS:** magnetic resonance spectroscopy
- ▶ **MS:** multiple sclerosis
- ▶ **MTI:** magnetisation transfer imaging
- ▶ **MTR:** magnetisation transfer ratio
- ▶ **SLE:** systemic lupus erythematosus
- ▶ **PD:** proton density
- ▶ **PML:** progressive multifocal leucoencephalopathy
- ▶ **PPMS:** primary progressive multiple sclerosis
- ▶ **VEP:** visual evoked potential

iii 13

represent more extensive tissue loss. FA is lower in acute, gadolinium enhancing lesions compared to non-enhancing lesions because extracellular oedema alters the anisotropic pattern of diffusion. ADC and MD values are raised, but the extent may depend upon the lesion age.

Changes in normal appearing brain tissue in MS patients have been detected by diffusion measures. As with MTI changes, these can occur early in the clinical course of MS and can precede new lesion formation. Several studies have reported a relation between DWI changes in normal appearing brain tissue and disability in different MS subtypes. DWI has not yet been included in clinical trials but may be useful in future studies of treatments which may prevent axonal loss.

The production of maps by DTI showing the principal direction of diffusion on a voxel by voxel basis allows the path of white matter tracts to be traced through the brain,



**Figure 2** Axial MRI of a 46 year old man with secondary progressive MS showing a large left sided periventricular lesion which is hyperintense with (A) T2 weighted imaging and hypointense with (B) T1 weighted imaging (“black hole”).

and this is known as tractography. This novel technique has emerging promise for investigation of white matter pathology in MS and other disorders.

### Magnetic resonance spectroscopy (MRS)

Proton magnetic resonance spectroscopy (MRS) enables the *in vivo* investigation of metabolic alterations associated with brain pathology, and provides a quantitative method for investigating the abnormalities in the normal appearing white matter. At longer MRI echo times, N-acetyl-aspartate (a neuroaxonal marker), creatine and phosphocreatine, and choline containing compounds may be quantified, while at shorter echo times additional metabolite peaks may be seen from myo-inositol (a potential marker of glial cells), glutamate and glutamine, and mobile lipids.

MRS studies in patients with established MS have demonstrated significant abnormalities in the concentration of metabolites in the normal appearing white matter, with notably reduced N-acetyl-aspartate, raised myo-inositol, and raised glutamate. A decrease in N-acetyl-aspartate is thought to indicate axonal dysfunction or loss, while an increase in myo-inositol has been proposed to reflect an increase in glial cell activity or numbers, and raised glutamate may have a role acutely in axonal injury. The stage at which these abnormalities first appear is less clear but two studies of patients with a CIS have shown separately that N-acetyl-aspartate is reduced and myo-inositol is raised. It is relevant to study this early phase of disease in order to search for prognostic markers for the future clinical course and to gain insights into early pathological processes.

### DISTRIBUTION OF LESIONS IN MS

#### Brain

Lesions can be seen anywhere in the brain parenchyma, but there are certain areas in which they are typical for MS.<sup>1</sup> Characteristic sites are in the periventricular region and juxtacortical white matter. The predilection for these sites may be explained in part by the distribution of venules where blood-brain barrier breakdown takes place. This concept is illustrated by the description of lesions arranged like fingers pointing away from the lateral ventricular walls which is also seen in pathological specimens where they are called “Dawson’s fingers”. These elliptical or ovoid lesions are believed to develop from demyelination along straight medullary venules arranged perpendicular to the ventricular walls; they are best seen on sagittal images where the common finding of lesions affecting the corpus callosum is also best seen. Juxtacortical lesions are often seen and are more suggestive of MS as they are uncommon with aging. Although current scanners do not commonly pick up grey matter lesions in the cortex, such lesions are seen in a significant number of postmortem brains from MS patients. Below the tentorium, the cerebellar peduncles and white matter, superficial pons, and floor of the fourth ventricle are common sites of lesions.

#### Optic nerves

The causative lesion of optic neuritis can usually be identified as an area of high signal on T2 or PD weighted imaging when appropriate fat and CSF suppression is applied. In theory, a clinically silent lesion in an optic nerve could provide evidence of dissemination in space, but this is not sought routinely because additional dedicated sequences are required to detect such nerve lesions reliably.

### Spinal cord

Spinal cord lesions are commonly seen in MS.<sup>4</sup> In fact, the presence of cord lesions is more specific for demyelination than in the brain because age related or non-specific ischaemic lesions are rare. T2 weighted imaging typically demonstrates small and circumscribed high signal lesions (fig 3). They tend to be aligned with the long axis of the cord and are usually less than two vertebral segments in length and involve less than half the axial cord area. On axial scans they may display a wedge appearance and reach the outer surface of the cord (fig 3). The lesions are not confined to white matter tracts and may also involve central grey matter. The cervical cord is most frequently affected and most lesions involve the dorsal or lateral cord. “Black holes” on T1 weighted imaging are not usually seen in the spinal cord but gadolinium enhancement of acute cord lesions does occur. Focal cord swelling can occur acutely but this invariably resolves. More diffuse abnormalities can be seen in disabled patients, particularly those with primary progressive disease which has a higher disease burden in the spinal cord.

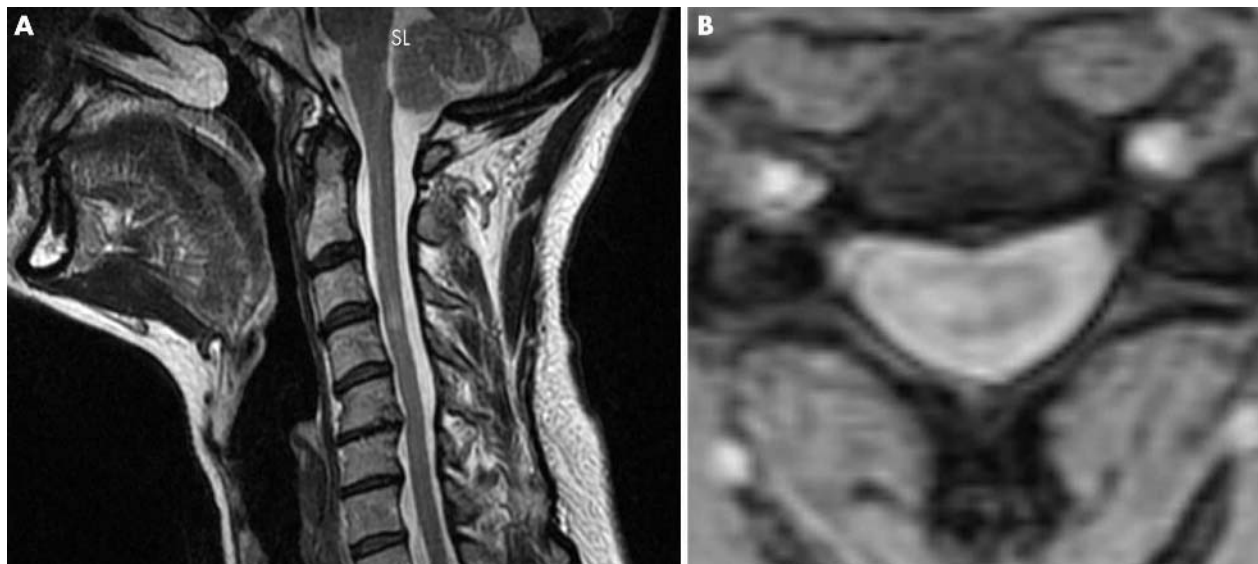
### Lesion dynamics

T2 hyperintense lesions can alter in size over the course of weeks and a proportion of their volume disappears because of resolution of oedema, although complete resolution is rare. Lesions can also cause local atrophy, a finding best appreciated in the optic nerve or spinal cord. About 50% of acutely T1 hypointense lesions resolve and this may be partly caused by remyelination. Gadolinium enhancement of acute lesions may appear as patchy, homogenous (involving the whole lesions, which is usually small), or ring shaped (often the ring is incomplete).

### VARIANTS OF MS

There are more aggressive forms of MS such as so called “tumefactive MS” which presents as a large high signal mass lesion sometimes requiring biopsy. Other terms that have in the past been included within the spectrum of inflammatory demyelination in the CNS include: Marburg’s disease, Balo’s concentric sclerosis, Schilder’s disease, acute disseminated encephalomyelitis (ADEM), and Devic’s neuromyelitis optica. Current evidence suggest that Marburg’s disease is MS in an unusually aggressive form and that the concentric zones of demyelination and myelination seen in Balo’s concentric sclerosis are an occasional finding in otherwise typical MS. Cases previously considered to have Schilder’s disease almost certainly had posterior hemispheric white matter demyelination caused by MS or adrenoleucodystrophy. Monophasic ADEM is not uncommon in children, and occasionally occurs in adults although much less frequently than MS. We doubt that recurrent ADEM exists in adults as an entity separate from MS and are concerned that such a diagnostic label may preclude patients receiving MS disease modifying treatments.

In its classical form, patients with Devic’s neuromyelitis optica have severe episodes of optic neuritis and transverse myelitis with variable recovery, longitudinally extensive spinal cord MRI lesions, normal brain MRI, and a moderate to pronounced CSF pleocytosis without oligoclonal bands. The suggestion that Devic’s syndrome is immunopathogenically distinct from MS comes from the recent observation by Lennon *et al*<sup>5</sup> that 70% of patients with the former condition have a serum autoantibody against CNS vascular and meningeal tissue components.



**Figure 3** Cervical spine MRI of a 49 year old woman with a spinal cord clinically isolated syndrome (CIS) demonstrating a lesion at C3/4 on (A) sagittal imaging and (B) axial imaging which shows that the lesion is on the right side of the cord.

### DIFFERENTIAL RADIOLOGICAL DIAGNOSIS OF WHITE MATTER LESIONS

White matter T2 hyperintensities in the brain are not specific to MS and are seen in a number of other disorders.<sup>1</sup> They can even be seen in otherwise normal individuals, particularly with increasing age. The challenge is to recognise the typical lesion morphology and distribution of MS lesions (brain and spinal cord) in conjunction with the characteristic clinical presentations.

#### Microvascular ischaemic lesions

These lesions are a common form of T2 hyperintense white matter lesions in the general population and are thought to be caused by ischaemic demyelination of the white matter. In addition, small vessel pathology, enlarged perivascular spaces, and sometimes infarcts can all give rise to T2 hyperintense white matter lesions. The frequency of microvascular ischaemic lesions increases with age. Of course, it is not simply the number but also the distribution and clinical context which determines their significance. The increase with age makes it difficult to assess MR imaging in the older patient who presents with a clinical picture suggestive of MS, particularly if lesions are present in sites typical of MS. In the young and the old, it is important to look for a history of risk factors for cerebral microvascular disease such as smoking, hypertension, diabetes, migraine, or potential for cardiovascular embolic disease. The lesions can be punctate or patchy and are more common in the supratentorial white matter where they can be present at any site, though most often are subcortical rather than periventricular. Infratentorial lesions are less frequent but can occur—for example, in the central pons as an area of high signal. Confluent high signal change is more common in the periventricular areas and the subcortical U fibres are typically spared. Microvascular ischaemic lesions are not seen in the spinal cord even with aging or vascular risk factors.

Although not related to ischaemic risk factors, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) can produce confluent subcortical white matter high signal which is usually

symmetrical and typically involves temporal poles and external capsules. These appearances are therefore not typical of MS and the clinical picture of strokes, migraine, cognitive impairment, and a dominant family history will also distinguish this condition.

#### Other inflammatory and vasculitic disorders

There are numerous disorders in this group that have MR appearances that could be mistaken for or even indistinguishable from MS.

Sarcoidosis can affect the CNS producing multiple lesions affecting the cortex, subcortical regions, cranial nerves, and rarely the spinal cord. The key distinguishing feature of this condition from MS is the presence of meningeal enhancement which is due to the granulomatous pathology. This finding highlights the importance of performing any repeat MR imaging with contrast *before* lumbar puncture as the latter can result in false positive meningeal enhancement on MRI.

Systemic lupus erythematosus (SLE) can present similarly to MS and may also have multiple small T2 signal intensities in the white matter. The MRI appearance is more suggestive of SLE when the lesions are not confined to periventricular white matter but favour the grey–white interface or even involve grey matter itself. The additional systemic clinical features and blood tests will help to distinguish SLE from MS.

Behçet's disease typically affects the diencephalon and brainstem but can also affect supratentorial white matter.

#### Infectious disorders

Two disorders in particular which are caused by an infectious agent can mimic MRI appearances of MS. Progressive multifocal leucoencephalopathy (PML) is caused by reactivation of latent JC polyomavirus in the immunosuppressed and is a multifocal demyelinating white matter disease. It causes confluent white matter lesions on MRI which do not cause mass effect or enhance. It is relentlessly progressive and usually fatal.

Neurological manifestations of Lyme disease can occur in association with white matter lesions similar to MS, although the usual clinical presentation is with a meningoradiculitis and/or cranial nerve involvement and an inflammatory CSF. The history of tick bite in an endemic area and serological investigation will help to distinguish Lyme disease from MS.

### Neoplastic disorders

MS can usually be easily distinguished from the appearances of a tumour, but occasionally large MS lesions can mimic a neoplastic disorder such as primary CNS lymphoma and even metastases or glioma. The clinical course and follow up imaging usually clarify the diagnosis, but biopsy may be required.

### Metabolic disorders

The inherited leucodystrophies are a group of rare white matter disorders which result in differing patterns of dysmyelination or demyelination. The MR appearances differ from MS in that the white matter changes are typically confluent and fairly symmetrical without the discrete, disseminated, focal lesions seen in MS. Adult onset disease occurs and can show regional changes on MRI. Adrenomyeloneuropathy often shows changes in the parieto-occipital lobe white matter, and Krabbe's disease (globoid cell leucodystrophy) can selectively affect the corticospinal tracts.

Central pontine myelinolysis results in T2 high signal in the central pontine fibres and occurs following an acute metabolic disturbance, typically rapid correction of hyponatraemia. Extra-pontine myelinolysis can also occur.

### ROLE OF MRI IN THE DIAGNOSTIC CRITERIA FOR MS

The clinical diagnosis of MS is based on a history of at least two separate episodes of focal neurological dysfunction supported by evidence of at least two lesions within CNS white matter which have been disseminated in space and time. The first set of criteria formalising the diagnosis of MS by Poser *et al*<sup>6</sup> in 1983 were created before the advent of MRI and the degree of diagnostic certainty was identified by categories ranging from a clinically definite diagnosis to laboratory supported definite MS, clinically probable MS, and laboratory supported probable MS.

During the 1980s and 1990s, MRI became increasingly available and was integrated into the investigation and diagnosis of patients thought to have MS. MRI criteria for the diagnosis of MS were developed by Barkhof *et al*<sup>7</sup> in 1997 and were later modified by Tintoré *et al*<sup>8</sup> in 2000. The Barkhof criteria<sup>7</sup> were developed in order to improve the prediction of a CIS converting to clinically definite MS on the basis of one MRI scan. A cumulative chance model with four criteria was used: (1) presence of at least one juxtacortical lesion; (2) at least one gadolinium enhancing lesion; (3) at least one infratentorial lesion; and (4) at least three periventricular lesions. These criteria were found to have a sensitivity of 82%, a specificity of 78%, and an accuracy of 80%. Tintoré *et al*<sup>8</sup> modified these criteria by allowing a substitution of one enhancing lesion by nine T2 lesions which was also predictive of conversion of a CIS to MS.

In 2001, the International Panel on the Diagnosis of MS published new guidelines for the diagnosis of MS which for the first time utilised MRI evidence of lesion dissemination in

time and space which could potentially allow the diagnosis of MS at an earlier stage.<sup>9</sup> These are commonly known as the McDonald criteria and incorporate the two previous sets of MRI criteria by Barkhof<sup>7</sup> and Tintoré.<sup>8</sup> The McDonald criteria,<sup>9</sup> like the Poser criteria,<sup>6</sup> rely on objective evidence of dissemination in space and time but accept that specific MRI abnormalities can provide evidence in patients with a CIS. The modified Barkhof-Tintoré criteria are used to provide evidence of dissemination in space. If these imaging criteria are not fulfilled, two T2 lesions plus the presence of oligoclonal bands can also provide evidence of dissemination in space, but this may lead to a reduction in accuracy of the diagnosis. The MRI criteria for the dissemination in time require the presence of a gadolinium enhanced lesion on an MRI scan done at least three months after the CIS, or a new T2 lesion confirmed on two MRI scans done at least three months after the clinical episode. These criteria have been shown in natural history studies to have a high specificity in predicting at three months and one year whether a patient with a CIS will develop clinically definite MS within three years.<sup>10</sup> If a new T2 lesion is allowed as evidence for dissemination in time at three months, specificity is maintained and sensitivity is increased. The McDonald criteria were also applied to the placebo arm of a CIS treatment trial (ETOMS trial) where it was found that the criteria for dissemination in space were associated with an increased likelihood of developing clinically definite MS. Figure 4 provides an approach for diagnosing MS after presentation with a CIS.

In brainstem CIS, the dissemination in space criteria are less specific than in other types of CIS in predicting conversion to MS because the presence of the symptomatic infratentorial lesion is not used to show dissemination in space.

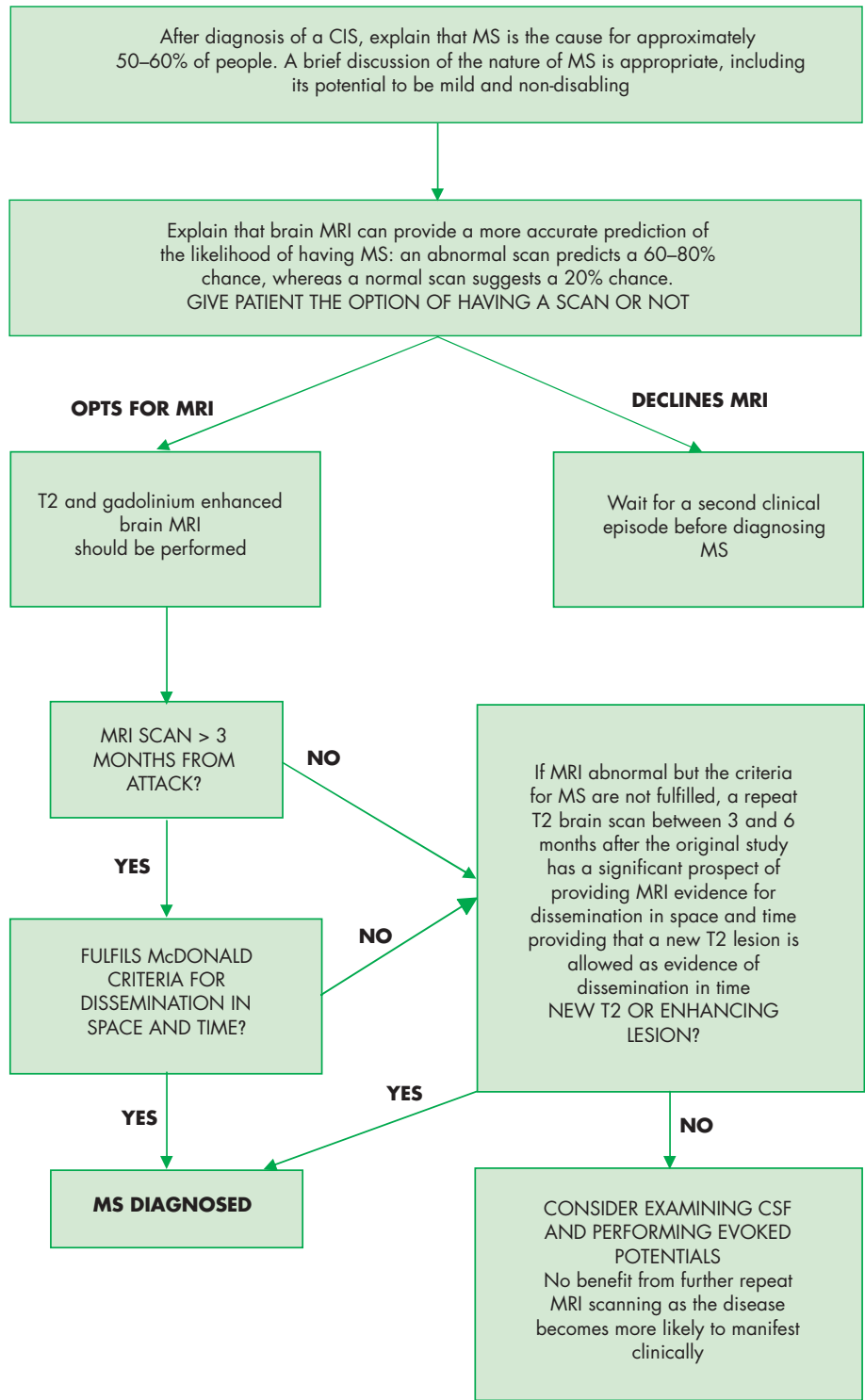
The potential for spinal cord MRI to aid diagnosis of MS is of interest because, as discussed earlier, the presence of asymptomatic cord lesions is rare in other disorders, and abnormalities in the spinal cord are common in patients with a new diagnosis of MS and thus are useful in providing evidence of dissemination in space. The McDonald criteria allow for the substitution of one brain lesion by one cord lesion.

### Diagnostic criteria for primary progressive multiple sclerosis (PPMS)

The clinical presentation of primary progressive multiple sclerosis (PPMS) makes the diagnosis more difficult than relapsing-remitting MS because the defining clinical relapses are absent, making it harder to define dissemination in time and space, and there are often fewer brain lesions with a greater disease burden in the spinal cord. Criteria for the diagnosis for PPMS are included in the McDonald criteria<sup>9</sup> and differ in that the presence of isolated oligoclonal bands in the CSF is a requirement. PPMS can be diagnosed when there is additional evidence of dissemination in space, using MRI or visual evoked potentials (VEPs), and in time, using MRI or progression of disability over one year.

### Revisions to diagnostic criteria

As this article goes to press, we are aware that the McDonald criteria are being revised; once published, the newly revised criteria will need to be considered in future diagnostic workup algorithms.



**Figure 4** Approach to the diagnosis of multiple sclerosis (MS) in a patient with a typical presentation of a clinically isolated syndrome (CIS). CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

**MRI ASSESSMENT OF PROGNOSIS**

Patients presenting with a CIS will often ask about the likelihood of developing MS in the future and also about the development of disability. The latter question is also relevant in patients who have recently been diagnosed with relapsing–remitting MS who have no significant disability. Several factors have a modest influence on prognosis including type of initial presentation and appearances on MRI scan.

The likelihood of subsequent development of MS has been addressed in natural history studies of CIS.<sup>10</sup> Based on data

from these studies, approximately 50–60% of all CIS patients will go on to develop MS in the long term. If an MRI scan at presentation is abnormal the likelihood of developing MS is increased to 60–80%, and if the scan is normal the risk is reduced substantially to approximately 20%. Patients with optic neuritis seem to have a lower risk of converting to MS in some studies where they have shown a lower frequency of MRI lesion than other types of CIS.

The prediction of subsequent disability has been assessed by comparing MRI findings at different time points with the

expanded disability status scale (EDSS). A normal MRI appearance at presentation with CIS is associated with a lower level of disability many years later. The number of abnormal lesions at baseline has been modestly related to the severity of subsequent disability, and there are also data to suggest that the distribution of lesions may be important, with infratentorial lesions being better predictors of disability. In one CIS cohort, the final level of disability after 14 years was correlated with the total lesion volume after five years and the increase in lesion volume occurring over the first five years. Subsequent changes in lesion volume were less informative. It has been concluded from these data that early lesion accumulation on MRI is related to future disability from MS, although the prognostic information is relatively weak.

### MONITORING DISEASE ACTIVITY IN CLINICAL TRIALS USING MRI

As well as being a diagnostic tool, serial MRI scanning can be useful as an objective measure to monitor lesion activity, lesion load, and response to treatment with disease modifying treatments in patients with MS. T2 lesions and “black holes” on T1 weighted imaging are used to measure lesion load, and gadolinium enhancing lesions measure new lesion activity. The number and volume of lesions are the most commonly used measures, but brain and spinal cord atrophy can also be used to monitor disease progression and may be more relevant when considering disability outcome in the longer term.

Exploratory studies of novel therapeutic agents normally have monthly scanning with gadolinium enhancement as the primary end point of treatment efficacy because clinical relapses will be relatively infrequent and disability progression will be minimal during short follow up periods. In larger phase III trials, T2 lesion number, T2 lesion load and atrophy, as well as enhancing lesions, are used as secondary outcome measures. T1 “black hole” lesion load can also be used and may be a better marker for axonal loss secondary to lesions if only persistent “black holes” are measured. Trials of patients with a CIS also employ MRI to select individuals at high risk of conversion to MS for enrolment.

The first trial to show a treatment effect using MRI outcome measures in patients with MS was the interferon beta-1b trial which found significant reductions in both new lesion activity and total T2 lesion load. MRI outcome measures have subsequently been included in all the major clinical trials evaluating the efficacy of disease modifying agents including trials of glatiramer acetate, interferon beta-1a, and mitoxantrone which is used in patients with aggressive disease. The most recent large trial was the AFFIRM study of natalizumab which demonstrated substantial reductions in relapse rate, disability, and MRI outcome measures which were of a higher magnitude than those seen in previous trials of existing disease modifying treatment.

Although conventional MRI outcome measures are used extensively in clinical trials, they must be used in conjunction with clinical and other para-clinical measures as they have been shown to be only modestly correlated with disease

progression. It is possible that the relation between MRI changes and clinical status may be confounded by the adaptive capability of unaffected areas of the CNS. Disease progression may only occur when pathology affects functionally important regions—for example, the spinal cord—and when the extent of pathology exceeds a critical threshold. The conventional MRI outcome lesion measures only assess pathology in white matter affected by lesions. The non-conventional MRI techniques discussed earlier have promise in assessing the pathological changes in normal appearing white and grey matter and could be incorporated into future clinical trials. Measures of brain atrophy are also now routinely included in treatment trials monitoring.

An exciting potential area for future study is to use MRI to monitor remyelination in experimental trials. MTR is higher in remyelinated than demyelinated lesions and may be a good tool for use in such trials. Another technique that shows promise in detecting myelin is the short T2 component of multi-exponential T2 relaxation.

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