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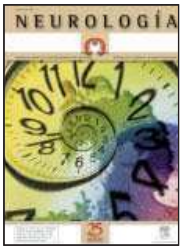

CONSENSUS DOCUMENT

Recommendations for using and interpreting magnetic resonance imaging in multiple sclerosis

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KEYWORDS
Multiple sclerosis;
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Abstract
Objective: To establish recommendations for using and interpreting magnetic resonance imaging (MRI) results in the diagnosis and follow up of multiple sclerosis (MS).
Method: Based on an extensive review of the literature and on their own experience, an expert group on MS produced a consensus on recommendations for using and interpreting MRI results in MS diagnosis and follow up.
Results: A brain MRI must be performed whenever possible in the initial diagnosis and assessment of patients suspected with MS. A spinal MRI study should be performed on all patients whose clinical onset shows signs of spinal cord syndrome, when the brain MRI findings are not very specific or when the brain MRI is normal in patients diagnosed clinically with MS. Cranial studies should be performed using appropriate repositioning techniques and different MR sequences, such as proton-density and T2-weighted fast spin-echo, and Fast-FLAIR. The use of contrast is mandatory whenever attempting to determine the temporal and spatial dissemination of demyelinating lesions for the initial diagnosis, or to determine inflammatory activity or lesion progression in follow-up studies.
Conclusions: The use of recommendations for using and interpreting MRI results in MS diagnosis and follow up should help to rationalise resources and optimise the clinical results arising from its practice.

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PALABRAS CLAVE
Esclerosis múltiple;
Resonancia magnética;
Recomendaciones

Recomendaciones para la utilización e interpretación de los estudios de resonancia magnética en la esclerosis múltiple

Resumen
Objetivo: Establecer unas recomendaciones para utilizar e interpretar la resonancia magnética (RM) en el diagnóstico y el seguimiento de la esclerosis múltiple (EM).
Método: Basados en una extensa revisión de la literatura y en su propia experiencia personal, un grupo de expertos en EM consensuaron unas recomendaciones con este objetivo.
Resultados: Siempre que sea posible se debe practicar un estudio de RM craneal en el diagnóstico o la evaluación inicial de los pacientes con sospecha de EM. Un estudio de RM espinal debe realizarse en todo paciente cuyo inicio clínico es un síndrome medular, cuando los hallazgos de la RM cerebral sean poco específicos o cuando el estudio de RM cerebral sea normal en pacientes diagnosticados clínicamente de EM. Los estudios cerebrales deben efectuarse con técnicas de reposicionamiento adecuadas y combinando secuencias ponderadas en densidad protónica, T2 y *fast*-FLAIR. Es obligado utilizar contraste siempre que se pretenda determinar diseminación temporal o espacial de las lesiones desmielinizantes para el diagnóstico inicial, o para determinar actividad inflamatoria o progresión lesional en los estudios de seguimiento.
Conclusiones: Disponer de unas recomendaciones para la utilización y la interpretación de los estudios de RM en el diagnóstico y el seguimiento de los pacientes con EM debe servir para racionalizar los recursos y para optimizar los resultados clínicos derivados de su práctica.

Introduction

Magnetic resonance imaging (MRI) is the most sensitive technique in the detection of demyelinating lesions of the central nervous system (CNS) in patients with multiple sclerosis (MS)[1]. As a result of this high sensitivity, MRI has become not only an essential technique in the diagnosis of MS, but also a prognostic marker in the initial phase of the disease, both in relation to the frequency and severity of future clinical recurrences and to the degree of future disability[2,3]. In addition, MRI contributes significantly to a better understanding of the natural history of MS and in the assessment of the effectiveness of new treatments[4,5].

The new diagnostic criteria proposed by McDonald et al.[6] attach great importance to MRI study findings. This is because they admit the possibility of establishing a diagnosis of MS in patients with a single clinical episode when the MRI shows demyelinating lesions in the CNS, which are disseminated in time and space.

The introduction in recent years of therapies that modify the course of the disease, especially from its earliest stages, make it necessary to establish recommendations on how to use and interpret MRI images effectively, not only during the initial diagnosis of the disease, but also in its monitoring[5]. The recommendations outlined in this document are intended for clinical practice and not for research studies or clinical trials in which the techniques used and the types of analysis to be performed are different[7,8].

MRI in patients with a first clinical episode with a probable demyelinating origin

A cerebral MRI should be obtained for all patients with a clinical condition indicative of a first bout of demyelinating origin. In this situation, the MRI should be performed on a preferential basis and, whenever possible, before starting steroid treatment, as this temporarily suppresses contrast enhancement of active lesions[9]. The purpose of this initial study is to identify the demyelinating lesions in the CNS and to determine their characteristics (topographical, morphological and numerical), as well as to exclude lesions with a non-demyelinating origin that may cause the symptoms.

Although orbital MRI is highly sensitive in detecting optic nerve affectation in the acute phase of optic neuritis, this exploration is not considered necessary to confirm this diagnosis, unless there are atypical or persistent clinical findings. In that case, the main purpose of the MRI is to discard causal processes with a non-demyelinating origin[10].

In patients in whom the case begins with a spinal syndrome, a spinal MRI should be performed in addition to the cerebral MRI to confirm the symptomatic demyelinating lesion and rule out causal lesions of a different origin. Spinal MRI (especially of the cervical segment) is also indicated when the cerebral MRI findings are inconclusive.

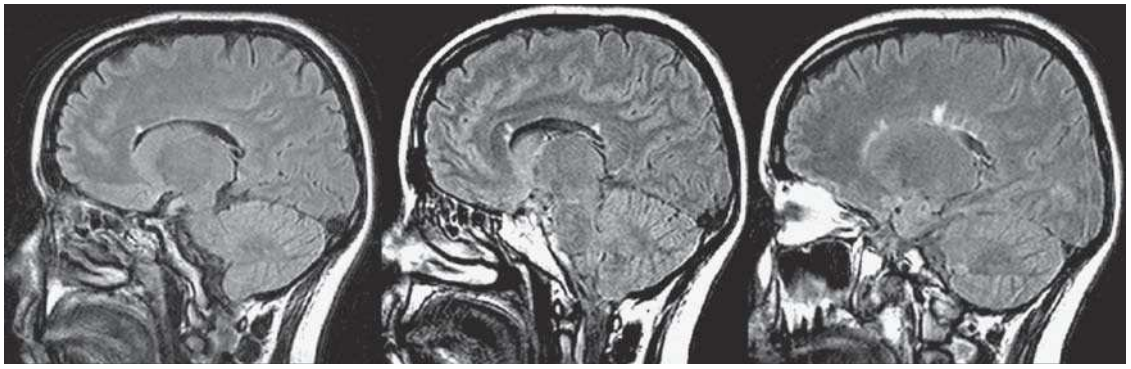

Figure 1 Brain magnetic resonance imaging. Sagittal fast-FLAIR sequence in a patient with a first clinical event of possible demyelinating origin. Periventricular hyperintense focal lesions can be observed, as well as in the subependymal area of the corpus callosum.

Recommendations for the use of MRI in relapsing-remitting forms of MS

In relapsing-remitting MS (RRMS), in which patients have presented outbreaks in different topographies and times, it would theoretically not be necessary to confirm the diagnosis by MRI. However, in our environment, where access to MRI is easy, establishing a diagnosis of MS without the support of a compatible MRI study has become questionable. Therefore, to confirm the clinical diagnosis of MS, performing a brain MRI study in all patients is strongly recommended. In addition, cranial studies must be complemented by a spinal cord study in the following cases:

1. Clinically diagnosed MS patients and those in whom the brain MRI study is normal. In these cases the detection of subclinical lesions with demyelinating characteristics in the spinal cord would support the clinical diagnosis[11].
2. Patients with clinical suspicion of MS in whom brain MRI findings are not conclusive in confirming the diagnosis. In these cases, identifying subclinical lesions with demyelinating characteristics in the spinal cord would support the diagnosis of MS[12].

MRI in primary progressive MS

It is essential to carry out a brain and spine MRI study on all patients who have been clinically diagnosed with primary progressive MS (PPMS) if there is no recent exploration. These studies are needed to exclude processes that may cause progressive disability (intraspinal tumour, spinal dural fistula, etc.) and to confirm the presence of demyelinating lesions. The presence of brain and spinal cord demyelinating lesions is part of the diagnostic criteria in this clinical form of MS[6,13,14].

Technical recommendations for MRI studies in MS

Studies should be carried out preferably in high-field devices (1.5T-3.0T), although middle-field devices (1.0T) are also acceptable.

In brain studies, rapid sequences (fast/turbo) for obtaining images proton density (PD) and T2 weighted (also called dual-echo [short and long] T2 sequences) are preferable to conventional spin echo sequences[15]. This is explained by the shorter acquisition time in the two former types, which minimise motion artefacts. Fast-FLAIR sequences can be used as a complement to T2 sequences; it is generally recommendable to obtain them in the sagittal and transverse planes because of their high sensitivity in detecting corpus callosum and juxtacortical lesions[16] (figs. 1-2). While some studies have shown the fast-FLAIR sequence to be more sensitive as compared with the dual-echo T2 sequence for detecting supratentorial lesions, it is clearly inferior for detecting infratentorial (fig. 3) and spinal cord lesions. Therefore, it is not advisable to use this sequence as a substitute for dual-echo T2 sequences[17]. A strategy offering maximum sensitivity in a reasonable time period is the combination of dual-echo fast-T2 and fast-FLAIR sequences[18].

In spinal studies, dual-echo T2-weighted conventional spin echo sequences are the most sensitive in detecting focal lesions in the sagittal plane. However, the artefacts caused by the pulsating movement of cerebrospinal fluid (CSF) and the spinal cord itself force these sequences to be obtained in synchronisation with the cardiac cycle or the peripheral pulse, which leads to excessively long acquisition times. The use of proton density-weighted and T2-weighted fast sequences appears to be less sensitive, but is also faster, does not require synchronisation with the heart or peripheral pulse and has sufficient diagnostic quality in a higher percentage of cases[19,20] (fig. 4). While some studies have shown STIR sequences to be more sensitive in detecting spinal cord lesions, these sequences often induce artefacts that lead to false positives, so their use in isolation is not recommended. The images obtained in the transverse plane must have a high resolution (voxel size, 3?1?1 mm). To reduce the artefacts derived from CSF pulsation in transverse imaging, it is advisable to use gradient echo sequences with short echo times in the cervical segment, although the use of T2-weighted fast sequences is also acceptable[20]. In the dorsal segment of the spinal cord, transverse images must be acquired with T2-weighted fast sequences with long echo times. Spinal studies benefit

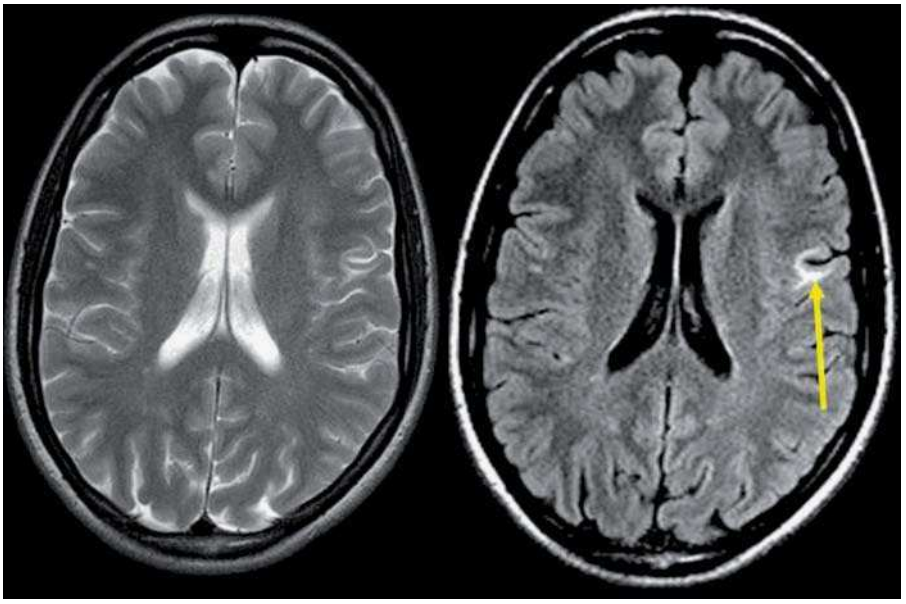

Figure 2 Brain magnetic resonance imaging. T2-weighted sequences with long echo time and transverse fast-FLAIR in a patient with clinically-defined multiple sclerosis. A left frontal juxtacortical lesion can be observed, which affects the U fibres. The lesion is observed better in the fast-FLAIR sequence (right) than in the fast-T2 sequence (arrow).

from the use of phase-array column coils[21], which enable complete images of the spinal cord to be obtained with a single sequence.

The in-plane resolution of images obtained in brain studies should be isotropic (1×1 mm) with a thickness between 3 and 5 mm (without separation). The sections obtained should cover the whole brain parenchyma; to do so, approximately 24 segments are required when using sections with a thickness of 5 mm and 42 when they have a thickness of 3 mm. The acquisition of 5-mm thick sections enables studies to be obtained in relatively quickly and is probably the strategy to use in most situations. Obtaining studies with contiguous 3-mm sections increases sensitivity in detecting small lesions, reduces the impact of the partial volume effect and facilitates co-registration between different sequences and their quantitative analysis. However, using 3-mm sections also increases the study time and decreases the signal/noise ratio in the images obtained. This increased sensitivity in detecting lesions with the use of 3-mm sections has not shown a significant impact on the diagnosis of the disease. Therefore, the decision to use 3 or 5-mm sections will depend on the type of analysis to be performed on the images obtained, although the use of 3-mm sections is recommended in studies belonging to serial studies that will be analysed quantitatively (lesion volume). In any case, patient diagnosis and monitoring must be carried out, whenever possible, with the same characteristics[7,22].

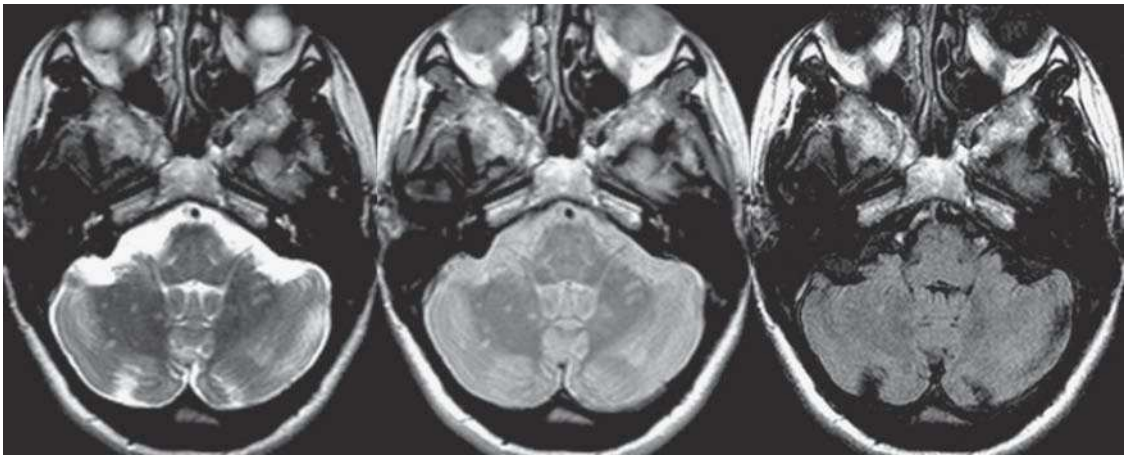

Figure 3 Brain magnetic resonance imaging. T2-weighted sequences (left), proton density (centre) and fast-FLAIR (right) in the transverse plane in a patient with clinically-defined multiple sclerosis. There are multiple small demyelinating lesions, many of which are not visible in the fast-FLAIR sequence.

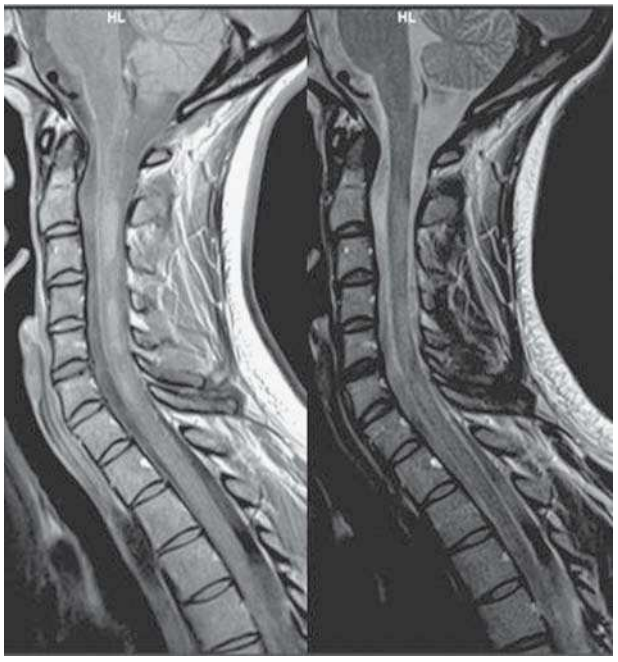

Figure 4 Spinal magnetic resonance imaging. Proton density-weighted sequences (left) and T2 sequences (right) acquired in the sagittal plane in a patient with clinically-defined multiple sclerosis, showing multiple small demyelinating spinal cord lesions. Proton-density sequences are very sensitive in the detection of lesions, showing hyperintensity in relation to the normal spinal cord tissue and cerebrospinal fluid. The T2 sequences provide its location within the spinal cord.

Recommended protocols

The recommended protocols for brain and spinal cord studies in initial diagnosis and monitoring vary according to the manufacturers and fields of MRI equipment. As a rough approximation, tables 1 and 2 show the more advisable sequences and technical parameters for 1.5T devices, which are the most commonly used in clinical practice.

Sequences in the sagittal plane should ideally cover the entire length of the spine. Additional sequences with reduced fields of view can be obtained for studies of spinal segments with high clinical suspicion of injury or to confirm lesions not well defined in whole-spine images. If the spinal study is performed after a brain study in which contrast has been administered, post-contrast T1 sequences must be obtained before dual-echo T2 sequences. In this situation, it is not necessary to obtain sequences before administering contrast.

Repositioning of brain MRI studies

The demonstration of temporal changes in demyelinating lesions (temporal spread in patients with suspected MS, and progression in lesion number and size in patients with MS) can be done by serial brain MRI studies. Visual or automatic analysis of changes in the number and volume of these lesions can be greatly hampered by differences in the positioning of the tomographic sections obtained between the different MRI studies being compared. Small variations in the repositioning of sections may hamper the visual detection of new or increased lesions and induce large variations in lesion volume quantification, which may exceed the variation expected in a year[23]. Therefore, it is essential to use a simple and reproducible repositioning technique, which even allows comparison of cranial MRI studies obtained at different centres.

The most commonly-used repositioning technique is that described by Gallagher et al.[24], with the only prerequisite being that it must be possible to obtain double-oblique tomographic planes. The use of 3-mm sections and head fastening elements during the exam helps to facilitate the repositioning of the studies and, therefore, to minimise errors in lesion quantification[25]. The technique of co-registration between sequences obtained at different times is a good strategy to avoid errors due to incorrect positioning[26].

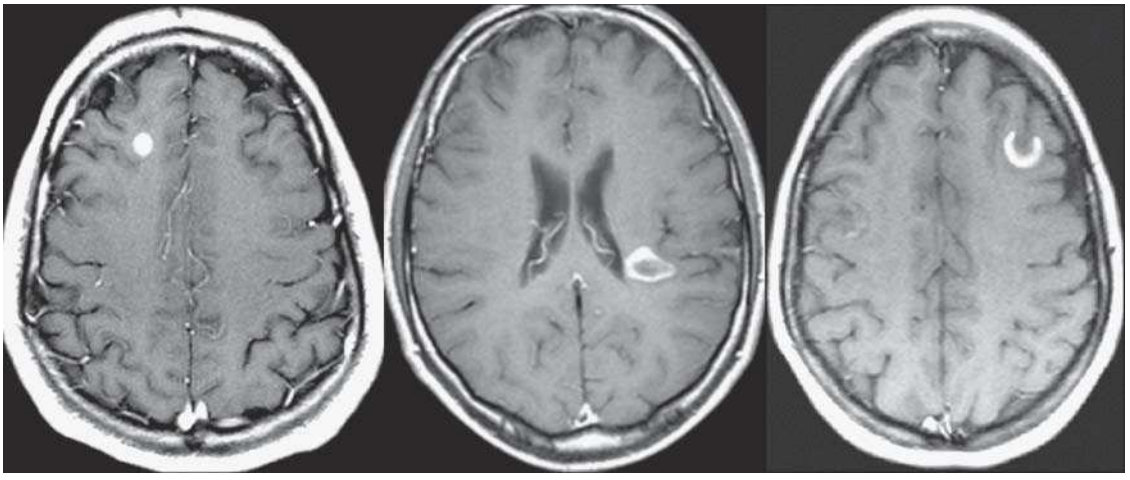

Figure 5 Brain magnetic resonance imaging (post-contrast T1-weighted sequences) in 3 different patients showing lesions with inflammatory activity. Note the different types of enhancement: nodular (left), ring (centre) and incomplete ring (right). The last enhancement pattern is very characteristic of inflammatory-demyelinating lesions.

Table 1 Magnetic resonance technique for brain studies (1.5T)

Parameters	Proton density or short-echo T2	T2	3D T1	T1	FLAIR	T1 gadolinium
Type of sequence	SE or *fast*-SE	SE or *fast*-SE	SPGR, MPRAGE, TFE	SE	*Fast*-FLAIR	SE
TR (ms)	2,800-4,000	2,800-4,000	Variable depending on the device	450-650	8,000-12,000	450-650
TE (ms)	14-20	80-120	Variable depending on the device	< 25	80-120	< 25
TI (ms)	—	—	Variable depending on the device	—	2,200-2,800	—
Orientation	Transversal oblique	Transversal oblique	Sagittal or coronal or transversal	Transversal oblique	Sagittal/ Transversal oblique	Transversal oblique
Number of sections	24-44	24-44	140-160	24-44	24-44	24-44
Acquisitions	2	2	1-2	1-2	2	2
Width (mm)	3-5	3-5	1-1.5	3-5	3-5	3-5
Separation (mm)	0	0	0	0	0	0
Flux compensation	Optional	Optional	—	No	Yes	Yes
Gadolinium	Can be obtained after administration of gadolinium	Can be obtained after administration of gadolinium	—	—	Can be obtained after administration of gadolinium	(0.2 ml/kg). Acquisition, 5-20 min alter gadolinium injection
Indication	Always	Always	Optional. If the aim is to carry out brain volumetric analysis	Always in the initial diagnosis, optional in monitoring	Always in the initial diagnosis, optional in monitoring	Always

In-plane resolution = 1 × 1mm.
Transverse oblique orientation: parallel to the subcallosal line.

Table 2 Magnetic resonance technique for spinal studies (1.5 T)

Parameters	Proton density or short echo T2	T2	T1	T2 (axial cervical)	T2 (axial dorsal)	T1 gadolinium
Type of sequence	SE o *fast*-SE	SE o *fast*-SE	SE	EG/ *fast*-SE	*Fast*-SE	SE
TR (ms)	2,800-4,000	2,800-4,000	450-650	700-900/ 2,800-4,000	2,800-4,000	450-650
TE (ms)	14-20	80-120	< 25	20-30/ 80-120	80-120	< 25
Orientation	Sagittal	Sagittal	Sagittal	Transversal	Transversal	Sagittal/ transversal
Number of sections	11	11	11	Variable	Variable	Variable
Acquisitions	2-4	2-4	2	2	2	2
Width (mm)	3	3	3	3	3	3
GAP (mm)	0	0	0	Variable	Variable	0/ variable
Gadolinium						0.2ml/ kg. Acquisition, 5-20min after injection
Cardiac synchronism	Required if SE sequences are used	Required if SE sequences are used	—	—	—	—
Indication	Always	Always	Optional	Optional. Confirm lesions identified in the sagittal plane or on spinal segments with high clinical suspicion	Optional. Confirm lesions identified in the sagittal plane or on spinal segments with high clinical suspicion	Optional. If the aim is to identify inflammatory activity

In-plane resolution = 1 × 1mm.
Sagittal sequences should ideally cover the entire length of the spine. Sequences can also be carried out with reduced fields of view for studies of spinal segments with high clinical suspicion of lesion or to confirm lesions not well-defined in whole-spine images. If the spinal study is performed after a contrast-enhanced brain study, then the post-contrast T1 sequences must be obtained before the dual-echo T2 sequences. In this situation, it is not necessary to obtain sequences before contrast administration.

Administration of contrast

The use of T1 enhanced sequences in combination with the injection of paramagnetic contrast (compounds containing gadolinium) allows selective identification of lesions with inflammatory activity[4] from the enhancement (hypersignal) that they present. This enhancement appears as an early and consistent event in MS lesions, and may adopt different forms[27] (nodular, complete ring, incomplete ring) (fig. 5) depending on the location on the demyelinating plaque of the areas with inflammatory activity. Incomplete ring enhancement is a very specific sign of demyelinating lesions, which is very helpful in differentiating tumour-like demyelinating lesions from tumours or infectious lesions. Those segments in the periphery of the lesion that show no enhancement coincide with the edge of the lesion in contact with the grey matter, where there is a lesser degree of inflammatory reaction.

Contrast enhancement of acute lesions is reversible and has an average duration of 3 weeks, although in 3% of cases it can be of more than 2 months[28]. This enhancement may occasionally reappear at the periphery of reactivated chronic lesions.

The use of sequences with contrast is relevant in initial disease diagnosis to demonstrate both spatial and temporal spread of the demyelinating lesions[6]. It is also relevant in follow-up studies that aim to assess the degree of inflammatory activity and lesion progression[3].

Guide to identify contrast-enhanced lesions[29]

A contrast-enhanced lesion is defined as an area with an evidently increased signal on T1 sequences in relation to the same area on a T1 sequence with the same characteristics obtained before administering contrast or, if this is not available, in relation to adjacent normal tissue (with a normal signal on T2 sequences). Small hyperintense foci (1 pixel) should not be considered as enhanced lesions, since they generally correspond to vascular structures.

Contrast-enhanced lesions are associated, in almost all cases, with hyperintense foci on T2 sequences. This condition is required when considering injuries in the posterior fossa and highly recommended at the supratentorial level. This condition is not essential in supratentorial lesions with cortico-juxtacortical location, where the sensitivity of T2 sequences is not as high. However, it is important not to confuse a contrast-enhanced lesion with a leptomeningeal vascular structure in the latter situation.

A contrast-enhanced lesion is defined as "new" when it is located on a lesion visible in T2 and was not enhanced in the previous study. In most cases, this lesion is also new in T2, although occasionally, an enhancement can be observed on a pre-existing lesion in T2.

A lesion is defined as having "persistent enhancement" when it was already identified in a previously-conducted MRI study. Typically, these lesions are associated with a persistent hypersignal on T2 sequences, but their size can vary.

Some demyelinating plaques may be partially or completely hyperintense on T1 sequences without contrast administration (fig. 6). The presence of these lesions is relatively common, especially in the secondary progressive forms, and they are associated with brain atrophy and disability[30]. The exact mechanism by which some lesions are hyperintense on T1 is not known, since no radio pathological correlation studies have been conducted. In any case, this fact makes it advisable to carry out T1 sequences without contrast before administering gadolinium, to avoid false positives in the interpretation of active lesions in post-contrast T1 sequences.

Flow artefacts may make the interpretation of contrast-enhanced lesions more difficult, especially in the posterior fossa. Enhanced lesions located in the posterior fossa

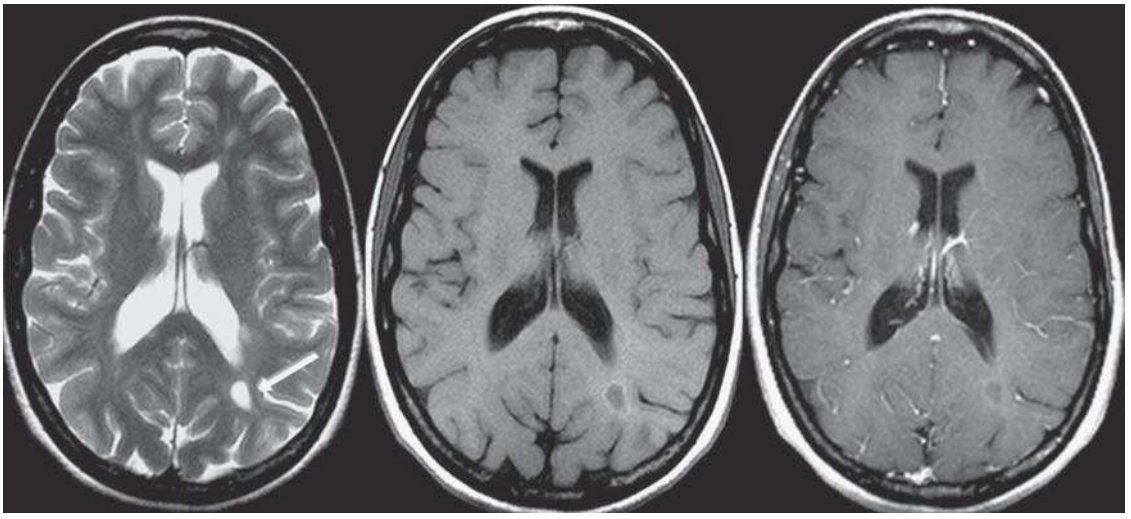

Figure 6 Brain magnetic resonance imaging. T2-weighted sequences (left), T1 (middle) and contrast T1 (right) in the transverse plane in a patient with secondary progressive multiple sclerosis. Note the posterior subcortical demyelinating lesion in the left cerebral hemisphere (arrow), which shows a hyperintense ring in the post-contrast T1 sequence. This lesion is not enhanced by contrast.

therefore need to be associated with a hyperintense area on T2, and post-contrast T1 sequences need to be obtained with flow compensation gradients (which minimise flow artefacts).

The evaluation of contrast-enhanced lesions can be carried out from the visual analysis of their total number (taking into account that a lesion identified in consecutive sections only counts as one) or by quantifying the number of areas that show enhancement. The latter method of quantification is closer to the volumetric analysis of enhanced lesions.

Type of contrast, dose and administration mode

The contrasts used in clinical practice are those that contain gadolinium, which is administered intravenously at a concentration of 0.5-1 mmol/ml, and at a dose of 0.1-0.2 mmol/kg of weight. The T1 sequence after intravenous contrast injection should be acquired at least 5-10 min after administration, and not later than 20 min. This time can be used to obtain fast-T2 or fast-FLAIR sequences, without affecting interpretation significantly.

Using a triple dose of contrast (0.3 mmol/kg) and/or obtaining a delayed T1 sequence (20-30 min) are strategies that, although they increase sensitivity in detecting enhanced lesions, also decrease specificity[31-33]. The increase in cost resulting from using these strategies, as well as the lack of data showing greater efficacy (diagnostic and prognostic) of these MRI studies, does not justify their use in general clinical practice.

Intravenous administration of compounds containing gadolinium is contraindicated or should be handled with caution in patients with severe renal insufficiency (chronic kidney disease in stages 3, 4 and 5) or those with acute renal failure, due to the risk of developing nephrogenic systemic fibrosis[34]. This risk is minimised by administering the minimal doses required (0.1 mmol/kg) and using compounds that have demonstrated the highest safety profiles. The administration of contrast in pregnant and nursing patients must also be assessed with caution, as gadolinium crosses the placenta and is excreted with milk. The contrast is thus incorporated by the foetus or ingested by the infant, who, having incomplete renal development, is subjected to a potential risk of nephrogenic systemic fibrosis.

Active lesions in T2 sequences

While active lesions are usually identified through the detection of contrast-enhanced lesions, they can also be identified through the detection of new lesions or those that increase in size on T2 sequences. The combined use of these two sequences (contrast-enhanced T1 and T2) increases visual detection of active lesions by up to 10-15% in relation to the isolated use of contrast-enhanced T1 sequences[9].

The use of T2 sequences in the detection of active lesions requires a strict adherence to recommendations that allow acceptable levels of precision and reproducibility to be achieved. Otherwise, an intraobserver reproducibility of only 33% has been reported[35]. Active lesions are identified from the joint visual analysis of dual-echo T2 sequences (short and long) obtained in both conventional and rapid technique sequences.

Proper repositioning between the scans to be compared is an essential prerequisite for identifying active T2 lesions.

General recommendations for identifying active T2 lesions[36]

It is advisable to adopt a generally conservative attitude in the identification of active T2 lesions to reduce the rate of false positives.

- Small hyperintense foci (<3 mm) should not be considered relevant.
- Areas where only a tenuous hyperintensity is identified in relation to the normal parenchyma should not be taken into account.
- The signal strength of a potentially active lesion should be greater than that of the adjacent grey matter in the short echo time, T2 sequence.
- In the event that a potentially active lesion is isointense in relation to adjacent grey matter in the short echo time, T2 sequence, it can still be considered as a lesion if its signal is clearly hyperintense in long echo times or if it is identified in two consecutive sections.
- Correct repositioning between studies to be compared is a critical factor when assessing active T2 lesions. If repositioning is suboptimal, adjacent cuts should be analysed in particular detail before classifying an injury as active, since rotational and parallel movements can cause apparent changes in lesion size and position.
- In patients with high lesion volumes, it is particularly difficult to detect active T2 lesions, especially if repositioning is not optimal. A particularly conservative attitude should be adopted in this situation.

Definition of active T2 lesions

"New" lesions: a "new" lesion is defined as a hyperintense area in T2 appearing in an area that was of normal tissue in a previous study with short echo time, T2 sequences. In general, it is recommended that this hyperintensity be confirmed in T2 sequences with both short and long echo times. This condition is a requirement for the anatomical regions most susceptible to flow artefacts, such as the temporal poles and the posterior fossa. A lesion can also be considered as "new" if it is adjacent to a pre-existing lesion but connected to it through an area with relatively low signal. In situations of suboptimal repositioning, "new" lesions can only be considered in areas with pre-existing lesions if they are confirmed in at least two consecutive sections. In the posterior fossa, any "new" lesion should be identified in the T2 sequences acquired with both long and short echo times. The latter are the most affected by flow

artefacts, so the detection of "new" lesions should be based on long echo sequences.

"Augmented" lesions: sometimes it is extremely difficult to determine whether a lesion has increased in size or whether its size or shape has merely changed as a result of suboptimal repositioning. For this reason, a lesion should never be considered as "augmented" if it has only changed its shape. Lesions larger than 5 mm in diameter should only be considered "augmented" if their diameter has increased by at least 100% or when an increase in size is detected in at least two consecutive sections. In lesions <5 mm, both criteria must be met to classify it as "augmented". Given the difficulty in fulfilling these criteria in potentially "augmented" lesions in the posterior fossa, this possibility should not be considered for lesions in this location.

Definition of the topographical and morphological features of demyelinating lesions detected by MRI

Identifying the characteristics of focal lesions detected on T2 sequences precisely is essential to determine the possibility of a demyelinating origin. In addition, topographical features help to determine the risk of an isolated clinical syndrome with probable demyelinating origin becoming MS in the future, since it is included within the McDonald diagnostic criteria[6]. It is therefore necessary to have definitions of the morphological and topographical features of demyelinating lesions that are as precise as possible.

Small hyperintense foci with a diameter less than 3 mm must be ruled out as lesions, especially if they are located in the subcortical white matter of the frontal lobes. Hyperintense foci attributable to Virchow-Robin perivascular spaces should also be excluded (they are isointense in the CSF on T2 sequences, both in long and short echo times).

Hyperintense lesions detected on T2 sequences are defined as follows[37]:

- Subcortical lesions: lesions located in the cerebral hemispheric white matter that have no contact with the ventricular surfaces or with the cortex.
- Cortical-juxtacortical lesions: lesions located in the cortical grey matter and/or juxtacortical white matter (U fibres) (fig. 2). It must not be forgot that myelin is also in the grey matter (although in a lesser proportion than in the white matter) and that, demyelinating lesions often also affect the cortical grey matter, both cerebral and cerebellar, for this reason. However, pure cortical lesions are very difficult to identify by MRI, probably due to their small size, to the scarce contrast shown relative to the CSF surrounding them and to the lesser inflammatory reaction that they present compared with those affecting white matter. Subcortical lesions differ from juxtacortical lesions in that the latter are in contact with the cortical grey matter, while in the former, the white matter is interspersed. Large periventricular lesions that reach the juxtacortical white matter peripherally should not be considered juxtacortical. The presence of at least one cortico-juxtacortical lesion is considered one of the diagnostic criteria proposed by Barkhof et al.[38] Fast-FLAIR sequences and, above all, DIR (double inversion-recovery) sequences are the most sensitive in detecting these lesions.
- Periventricular lesions: lesions in contact with the lateral ventricles or more rarely with the third ventricle. Infratentorial lesions that are in contact with the surface of the fourth ventricle are not considered periventricular. The presence of at least three periventricular lesions is considered one of the diagnostic criteria proposed by Barkhof et al.[38]
- Corpus callosum lesions: focal lesions that can also be periventricular. Sagittal Fast-FLAIR sequences are particularly sensitive in detecting these lesions (fig. 1). In this plane, the lesions need to be placed in the medial two-thirds of the corpus callosum to avoid including the paracallosal areas. Transcallosal bands are identified as lines that traverse the corpus callosum (optimally observed in transverse T2 sequences), and that correspond to a Wallerian degeneration of the corpus callosum secondary to paracallosal lesions. These bands should not be considered as corpus callosum lesions.
- Thalamic or basal ganglia lesions: lesions clearly located within the sinus of grey nuclei. Lesions affecting white matter tracts and that make marginal contact with the nuclei should not be included.
- Infratentorial lesions: lesions located in the cerebellum, midbrain, pons or medulla oblongata. Due to the frequent artefacts existing in the posterior fossa, these lesions must be identified in both the short and long echo times of T2 sequences. Fast-FLAIR sequences are less sensitive than dual-echo fast-T2 sequences in the identification of infratentorial lesions (fig. 3). The presence of at least one infratentorial lesion is considered as one of the diagnostic criteria proposed by Barkhof et al[38].
- Ovoid lesions: ovoid lesions with their major axis oriented in a perpendicular direction to the ventricular wall[39]. They correspond to lesions with a perivenular location (Dawson's fingers). Their presence should be analysed exclusively in images acquired in the transverse plane (fig. 7).
- Large lesions: lesions with a diameter >6 mm, excluding the lines parallel to the ventricular walls and the transcallosal bands.
- Black holes: T1 hypointense lesions (in sequences obtained with spin echo) in relation to the normal grey matter with a persistence of at least 6 months and always associated with an area of T2 hyperintensity (fig. 8). Although these injuries were previously considered to correspond to demyelinating lesions with a strong tissue destruction component (low axonal density), recent histopathological correlation studies have shown a great variability in their pathological substrate[40]. Their presence is more common in patients with progressive forms of MS, especially at supratentorial level, while their detection is generally scarce at the infratentorial and spinal level[41]. Lesions that have the above characteristics, but that show total or partial post-contrast enhancement (usually peripheral) should not be considered as black holes. These pseudo-"black holes" are active lesions with an oedematous and demyelinating component, whose size and hyposignal on T1 can be reduced or disappear after

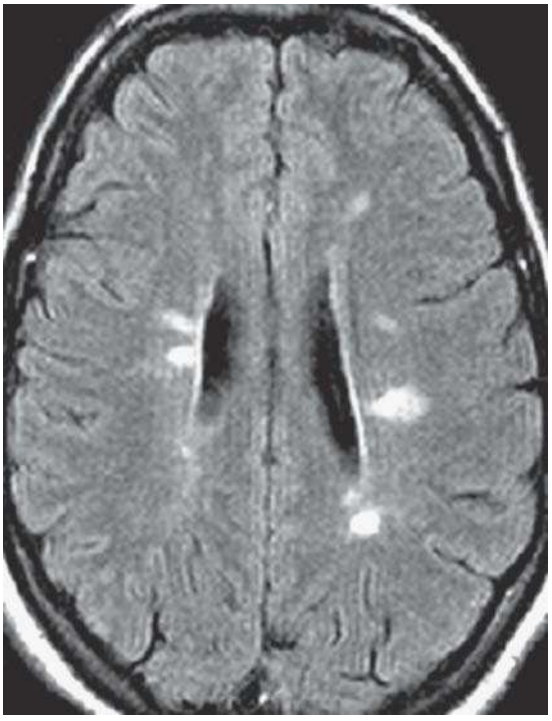

Figure 7 Transverse fast-FLAIR sequence in a patient with clinically-defined multiple sclerosis. There are characteristic lesions in periventricular location (some ovoid), with their major axis perpendicular to the ventricular walls.

the resolution of inflammatory activity (cessation of contrast enhancement) and development of remyelination. In contrast, "chronic" black holes are irreversible and their number and volume have been related to the degree of disability, so these parameters have been used as a marker of progression of the neurodegenerative component of the disease. Some immunomodulatory drugs decrease the proportion of lesions active with gadolinium that become chronic black holes.

- Pseudo-tumoral lesions: there is no set minimum diameter at which a focal demyelinating lesion is considered pseudo-tumoral, although this could be established around 3 cm. A lesion area resulting from the confluence of multiple lesions should not be interpreted as a pseudo-tumoral lesion. Pseudo-tumoral lesions correspond to active lesions, generally with a hemispheric cerebral location that can cause clinical symptoms indicative of an expansive process, but they can also be asymptomatic. In some cases, it can be very difficult to differentiate pseudo-tumoral lesions from tumoral or infectious lesions. In these cases, the clinical context, the presence of incomplete ring enhancement (fig. 9) or a Balo-type lesion pattern (concentric rings) (fig. 10) and the detection of additional lesions with demyelinating features in the remaining brain or spinal cord tissue are the most valuable data for establishing a correct differential diagnosis. Obtaining diffusion sequences and a localised proton spectroscopy examination of the lesion may sometimes be a diagnostic aid to differentiate tumoral processes or abscesses.
- Dirty-appearing white matter: focal or diffuse areas with discrete hyperintensity in T2 sequences, in relation with normal white matter, located in the white matter proximal or not to subcortical focal lesions and that predominantly, and sometimes symmetrically, affect the deep periventricular white matter of the cerebral hemispheres, especially in patients with progressive forms of MS (fig. 11). Its signal is less intense than that of focal lesions and is close to that of cortical grey matter. These areas, which must be at least 10 mm in diameter and which must be identified in at least two consecutive transverse sections, represent a diffuse component of the demyelinating and axonal damage process[42]; on occasion, they can be difficult to differentiate from normal white matter, so their isolated presence should not be regarded as an abnormal finding.
- Spinal cord injuries: spinal cord injuries are very common in patients with MS and their detection increases the sensitivity and specificity of MRI studies. Lesions in this

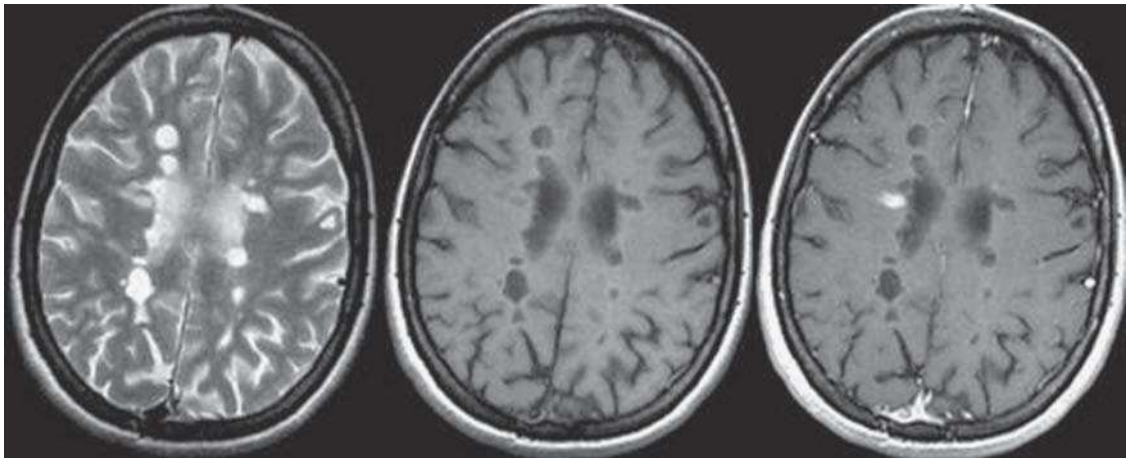

Figure 8 Brain magnetic resonance imaging. T2-weighted sequences (left), T1 (middle) and post-contrast T1 (right) in the transverse plane in a patient with secondary progressive multiple sclerosis. Note how many of the lesions visible on T2 sequences are hypointense on T1 sequences, showing no post-contrast enhancement (irreversible black holes).

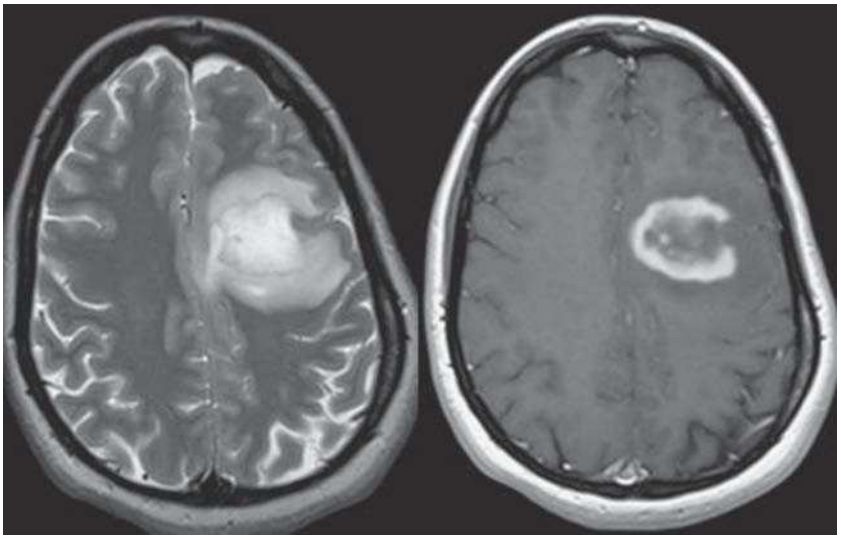

Figure 9 Brain magnetic resonance imaging. T2-weighted sequences (left) and contrast T1 (right) in the transverse plane in a patient with a pseudo-tumoral lesion of demyelinating origin. Note that the lesion shows an incomplete ring enhancement with its open margin in contact with the cortical grey matter (courtesy of Dr. Marzo).

area must have certain characteristics to be considered typical of MS: being hyperintense in T2-weighted sequences, being more than 3 mm in diameter, but with a craniocaudal extension less than two vertebral bodies, producing no significant swelling of the spine (with the exception of some acute phase symptomatic lesions) and affecting the transversal spinal area incompletely[14].

Double inversion-recovery sequences

Double inversion-recovery (DIR) sequences have recently been introduced in the technical arsenal of MRI. These sequences use a double saturation pulse that cancels the signal from the CSF and the white matter[43]. As a result, white matter appears hypointense, allowing greater contrast with demyelinating lesions (hyperintense). DIR sequences improve the contrast of cortico-juxtacortical[44] and infratentorial lesions and increase sensitivity in detecting these lesions compared with conventional sequences (dual-echo fast-T2 and fast-FLAIR). Their limited availability in current devices and a low signal to noise ratio, which requires relatively long acquisition times, are factors that have limited their application in clinical studies.

High field MRI (3.0 T)

One way to increase MRI sensitivity in detecting demyelinating CNS lesions is through the use of high-field devices (3.0T). These devices can detect 20-50% more

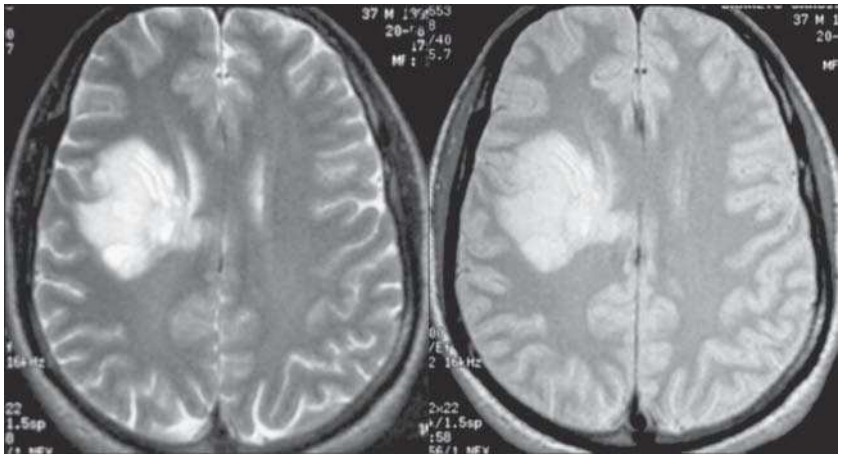

Figure 10 Brain magnetic resonance imaging. T2-weighted sequences (left) and proton density (right) in the transverse plane in a patient with a pseudo-tumoral lesion of demyelinating origin. Note the pattern of concentric bands within the lesion (Balo-type pattern).

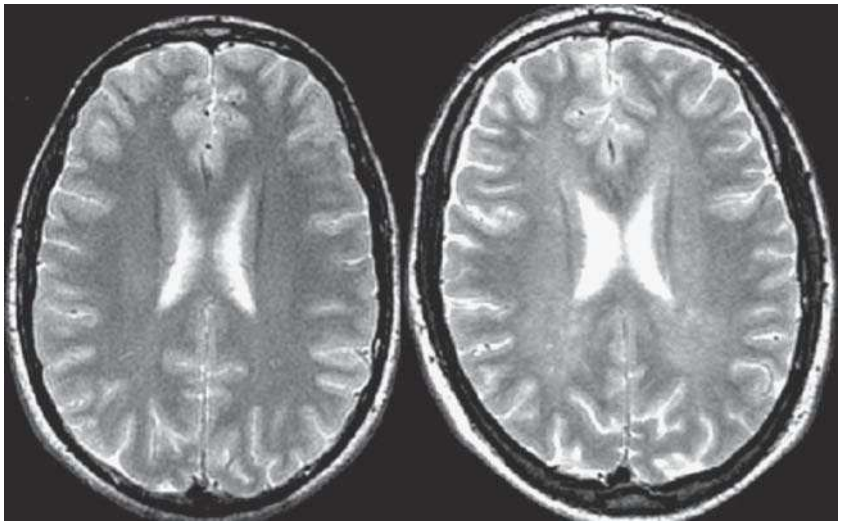

Figure 11 Brain magnetic resonance imaging. Transverse T2-weighted sequences in a healthy subject (left) and in a patient with multiple sclerosis (MS) (right). Note the discrete diffuse hypersignal shown by the hemispheric white matter in the patient with MS (dirty-appearing white matter).

gadolinium-enhanced or hyperintense lesions in T2 compared with 1.5T MRI devices[45,46]. However, there is no evidence to suggest that this increased sensitivity has an impact on therapeutic decisions in patients with established MS. In patients with an isolated neurological syndrome, the increased sensitivity of 3.0T devices lets the criteria for space and time dissemination be established more frequently, and this could influence early treatment of a greater number of patients[47]. Fast-FLAIR sequences benefit especially from the 3.0T fields, as their sensitivity in detecting infratentorial lesions is increased. On the other hand, the effect of high fields in T1 sequences is negative, especially when using spin echo sequences (longitudinal relaxation times are extended and, therefore, tissue contrast is reduced). It is thus advisable to replace them with gradient echo sequences[48].

Non-conventional MRI techniques for MS diagnosis and monitoring

In recent years, a major effort is being made in the development and clinical application of new MRI techniques that allow specific, simple and reproducible detection of macroscopic or microscopic lesions whose pathological substrate correlates better with the degree of clinical disability, such as severe demyelination and axonal destruction.

These techniques include the estimation of the degree of axonal damage from the quantification of N-acetylaspartate concentration obtained by proton spectroscopy, the calculation of cerebral volume and spinal cord transverse area as a measure of atrophy, the quantification of myelination degree from the magnetization transfer ratio, and the use of diffusion sequences that partially characterise macroscopic and microscopic lesion substrates and that measure axonal fibre integrity and organisation. Lastly, functional MRI can be used in patients with MS to evaluate the effect of brain neuroplasticity, which would at least partially explain clinical-radiological dissociation in these patients.

However, the profitability of these unconventional techniques in MS diagnosis and monitoring is limited outside of experimental studies or clinical trials. Their use is generally not justified in either diagnostic or monitoring MRI studies in clinical practice[5,49-51].

Proton spectroscopy

Proton magnetic resonance spectroscopy (MRS) is a technique that allows biochemical information to be obtained from pathological alterations in lesions visible on T2 sequences and in apparently normal tissue. There is some controversy in the literature regarding the diagnostic value of MRS in the study of pseudo-tumoral lesions of demyelinating origin to differentiate them from tumours. Some authors suggest that there are not enough differences in the spectral pattern between the two processes (reduction of N-acetyl aspartate, elevation of choline and lipids)[52,53]. Others do find sufficient differences, especially when using different echo times and when performing a quantitative analysis of different metabolites[54-56]. Therefore, while MRS can be used in selected cases to characterise pseudo-tumoral lesions, one must be cautious when making diagnostic and therapeutic decisions based solely on these findings. The technique is capable of detecting biochemical changes in normal-appearing white matter in MS patients, so these data have been used to evaluate disease progression in experimental studies. The technical complexity of MRS studies, their limited reproducibility and their cost in time have prevented MRS from being a technique of clinical utility in patients with MS. Results from clinical trials with small patient groups have also been contradictory about

the effect of immunomodulatory drugs. There is thus insufficient data to justify the use of MRS in the diagnosis and monitoring of patients with MS. Some guidelines for obtaining multicentre MRS studies[57] that attempt to standardise the studies conducted at different centres have recently been published.

Cerebral volume

It is well established that patients with MS develop brain atrophy progressively. The mechanisms by which this progressive atrophy occurs are not fully understood, although it seems clear that it is mostly a consequence of axonal and myelin loss. The relation between focal brain tissue lesions and atrophy is not well determined, as there is a time lag between the progressive development of atrophy and the volume of focal lesions. This dissociation suggests that there are other mechanisms involved in the development of atrophy, such as a diffuse microscopic alteration in the white matter and in the cortical and subcortical grey matter.

The quantification of brain atrophy by MRI is used as a measure of the degree of loss of brain tissue in patients with MS[49,58,59]. Longitudinal studies have shown that the degree of atrophy progresses in some patients, and that this progression correlates with a worsening of disability. The measurement of brain volume can be calculated in a relatively simple way by obtaining T1-weighted images to which automatic segmentation programs are applied; the programs define the contours of the brain parenchyma and extract the ventricular volume, thus returning quantitative, accurate and reproducible data on the volume of brain parenchyma.

Reactive astrocytosis is a phenomenon that could mask the detection of brain atrophy in MS, as a result of increased brain volume. Moreover, the degree of atrophy may be biased by fluctuations in the concentration of water attributable to both active lesions and the anti-oedema and anti-inflammatory effect of certain treatments (corticosteroids, immunomodulators). These factors influencing the measurement of brain volume probably make this parameter underestimate the true extent of axonal damage, especially in early disease stages.

The loss of brain volume (approximately 4 times higher in MS patients than in the normal population) occurs primarily at the expense of grey matter, even in the early stages of the disease. Compared with the overall cerebral volumetric analysis or selective analysis of white matter, selective volumetric analysis of grey matter is better correlated with the degree of disability and the presence of neurocognitive impairment in patients with MS[60,61]. In addition, the detection of grey matter atrophy is the only quantitative method to assess cortical damage in patients with MS through MRI, given the insensitivity of conventional techniques in the detection of lesion extension in this case. It therefore seems that brain volumetric studies should be performed selectively on grey matter, requiring programs that can perform automatic segmentation (fig. 12). However, the precision of these selective measurements can be altered by demyelinating lesions in the white matter, because segmentation programs often incorrectly classify them as apparently normal grey matter[62], and cause false increases in the volume of grey matter with the progression of the disease. Therefore, these programs should be applied with injury masking, which slows the process, making them difficult to apply in clinical practice. Quantification of brain atrophy is also relatively insensitive to changes over time (of approximately 1-2% annually in the different disease phenotypes)[63,64], so it does not seem a useful measure in the individual assessment of the effect of treatment, at least in the short to medium term.

Spinal area

Spinal atrophy is a relatively frequent finding in progressive forms of the disease. This atrophy is most evident in the cervical segment and bears no relation to lesion volume in T2, both cerebral and spinal. The most likely source of spinal atrophy is axonal destruction secondary to Wallerian degeneration. Different studies have shown that the degree of cervical spinal atrophy significantly correlates with the degree of neurological disability, with the correlation obtained improving significantly with measures of volume or number of lesions on T2, both cerebral and spinal. Spinal atrophy can be quantified in the cervical segment from transverse three-dimensional T1-weighted images with which transverse reconstructions can be performed on the C2-C3 segment in which its area is calculated[65].

Transfer of magnetization

This MRI technique allows quantitative data to be obtained from the magnetization transfer ratio (MTR), which indirectly measures the degree of myelination of both macroscopic demyelinating plaques and normal-appearing white matter[66-68]. Some studies have shown that MTR values vary with the evolution of demyelinating plaques, and this variation is attributable to the increase in the degree of demyelination (decreased MTR values) or to the development of remyelination (increased MTR values)[69,70]. This ability of MTR values to objectify the degree of longitudinal myelination of a plaque makes it possible to use this technique for analysing the potential neuroprotective effect of new treatments. However, its use in MRI for diagnostic and monitoring of individual MS patients is not justified, because its diagnostic and prognostic value has not been proven[50,51].

Diffusion MRI

Diffusion sequence by MRI can be used in addition to conventional sequences in diagnostic studies to characterise focal demyelinating lesions in which acute or infectious (abscesses) vascular lesions are included in the differential diagnosis. The diffusion tensor images make it possible to analyse the organization and integrity of brain and spinal cord axonal fibres in patients with MS, using various

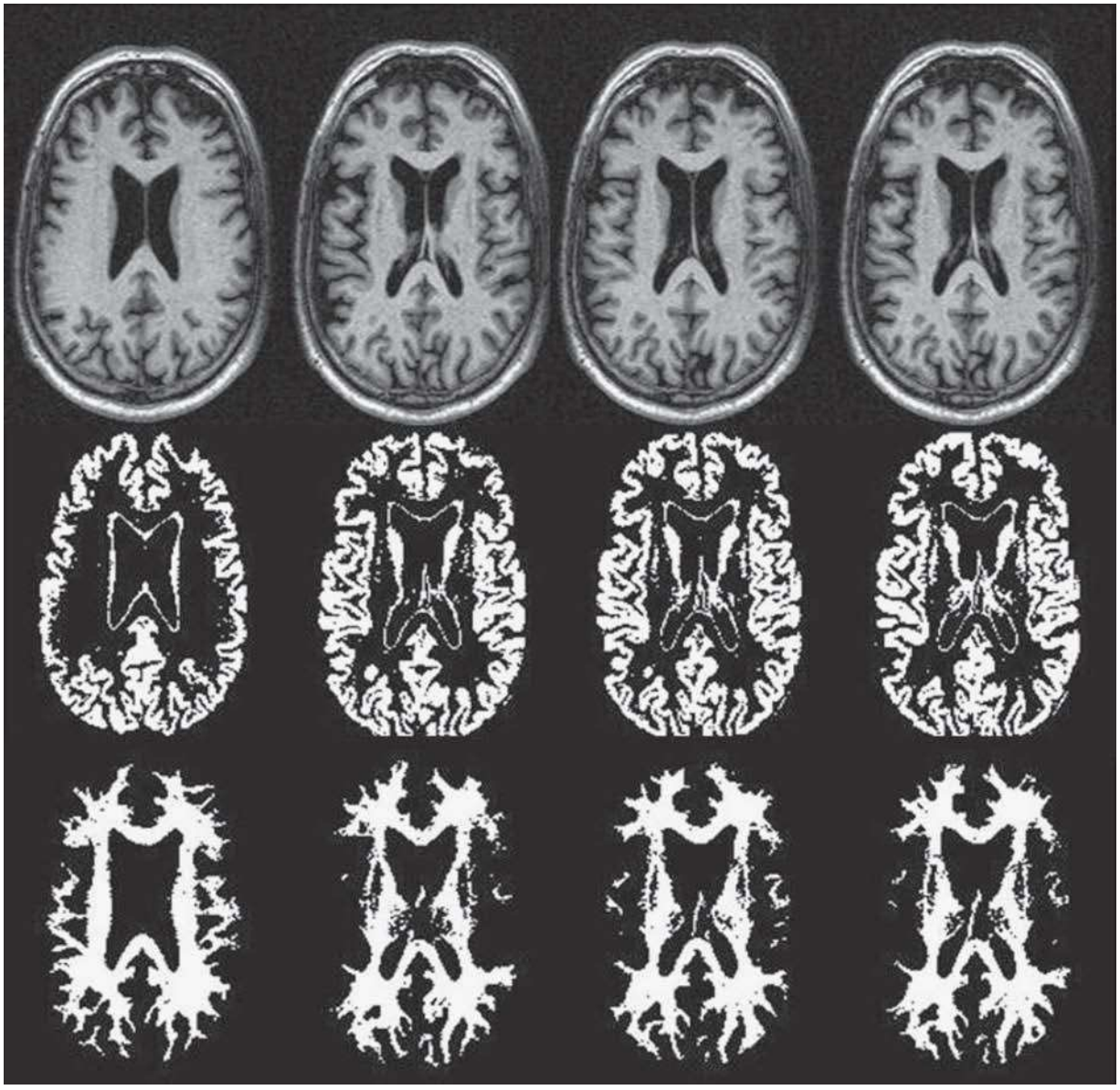

Figure 12 Automatic cerebral region segmentation. From T1 sequences (top row), programs are applied to make it possible to obtain a selective volumetric analysis of grey matter (middle row) and white matter (bottom row).

parameters such as mean diffusivity and anisotropy fraction[71], and to study subtle changes that take place in normal-appearing white and grey matter[72]. These variables have shown good correlation with the degree of disability and cognitive impairment. However, there are no studies that demonstrate the usefulness of this MRI technique in MS diagnosis and monitoring[50,51].

Diffusion MRI also makes it possible to obtain axonal maps (tractography) and thus provides information on the organisation of cortical connections and their projections in the white matter. This technique lets researchers visualise white matter tracts, both cerebral and spinal, and can objectify changes in their integrity that are not detectable with conventional sequences, and that could explain certain clinical manifestations[73] (fig. 13). Its current value is essentially limited to research studies.

Functional MRI

Functional MRI (fMRI) is a non-invasive MRI technique makes it possible to visualise brain areas activated in relation to a specific task or stimulus. The most common clinical use of fMRI is presurgical identification of critical functional areas, to facilitate performing a surgery as functional as possible. The technique is also being used in studying normal functional anatomy and investigating the phenomenon of neuroplasticity in both healthy subjects and in patients with various neurological or psychiatric processes, among which MS must be highlighted. In patients with different MS phenotypes and degrees of disability, fMRI shows changes in the pattern of cortical activation in motor, sensory and cognitive paradigms, which probably reflect a functional reorganisation of the brain in response to tissue injury[74]. These changes include an

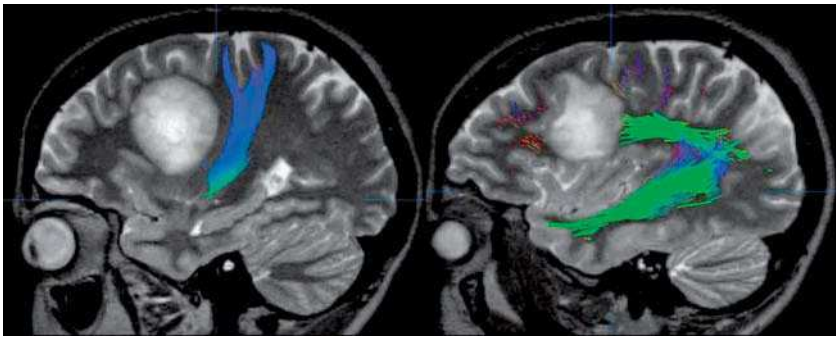

Figure 13 MRI tractography performed on a patient diagnosed with a left frontal pseudo-tumoral demyelinating lesion that produced an interruption of the arcuate fibres (right), but did not affect the corticospinal tract (left). The patient presented conduction aphasia without motor deficit.

increase in the intensity of normal brain activation and the recruitment of structures not normally activated. These findings, which have been interpreted as adaptive or compensatory events, seek to minimise the degree of motor and cognitive disability attributable to irreversible neuro-axonal damage, and would at least partially explain the clinical-radiological dissociation between the extent and severity of neuro-axonal damage and disability in these patients. These cortical hyperactivity patterns may vary over time in relation to a depletion of cortical reorganisation capacity and can be modulated with pharmacological and rehabilitation therapies[75]. In the future, fMRI might be used as a substitute marker for the evaluation of the effectiveness of therapies that modulate or promote the neuroplasticity phenomenon.

Conclusions

Magnetic resonance imaging is a highly sensitive and relatively specific technique for identifying demyelinating lesions in the CNS. A correct analysis of the studies offers diagnostic and prognostic information, but the information obtained from the pathological substrate of the lesions is still limited, even with non-conventional MRI techniques, which as yet have virtually no diagnostic or prognostic value.

The use of MRI in the diagnosis and monitoring of MS patients in clinical practice should be carried out under appropriate technical conditions and with correctly established indications. This should serve to rationalise resources and improve the clinical efficacy derived from MRI studies.

Conflict of interests

The authors declare no conflict of interests.

References

1. Fazekas F, Barkhof F, Filippi M, et al. The contribution of magnetic resonance imaging to the diagnosis of multiple sclerosis. Neurology. 1999;53:448-57.
2. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med. 2002;346:158-64.
3. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology. 2006;67:1242-9.
4. Miller DH, Runge P, Johnson G, et al. Serial gadolinium enhanced magnetic resonance imaging in multiple sclerosis. Brain. 1988;111:927-39.
5. Filippi M, Dousset V, McFarland HF, Miller DH, Grossman RI. Role of magnetic resonance imaging in the diagnosis and monitoring of multiple sclerosis: consensus report of the White Matter Study Group. J Magn Reson Imaging. 2002;15:499-504.
6. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50:121-7.
7. Filippi M, Horsfield MA, Ader HJ, et al. Guidelines for using quantitative measures of brain magnetic resonance imaging abnormalities in monitoring the treatment of multiple sclerosis. Ann Neurol. 1998;43:499-506.
8. Miller DH, Grossman RI, Reingold SC, McFarland HF. The role of magnetic resonance techniques in understanding and managing multiple sclerosis. Brain. 1998;121:3-24.
9. Miller DH, Barkhof F, Nauta JJ. Gadolinium enhancement increases the sensitivity of MRI in detecting disease activity in multiple sclerosis. Brain. 1993;116:1077-94.
10. Rocca MA, Hickman SJ, Bö L, Agosta F, Miller DH, Comi G, et al. Imaging the optic nerve in multiple sclerosis. Mult Scler. 2005;11:537-41.
11. Thorpe JW, Kidd D, Moseley IF, et al. Spinal MRI in patients with suspected multiple sclerosis and negative brain MRI. Brain. 1996;119:709-14.
12. Bot JC, Barkhof F, Lycklama à Nijeholt G, et al. Differentiation of multiple sclerosis from other inflammatory disorders and cerebrovascular disease: value of spinal MR imaging. Radiology. 2002;223:46-56.
13. Thompson AJ, Montalban X, Barkhof F, et al. Diagnostic criteria for primary progressive multiple sclerosis: a position paper. Ann Neurol. 2000;47:831-5.
14. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005;58:840-6.
15. Patola WB, Coulter BA, Chipperfield PM, Lingawi SS. A comparison of conventional spin-echo and fast spin-echo in the

detection of multiple sclerosis. J Magn Reson Imaging. 2001;13:657-67.
16. Hashemi RH, Bradley WG, Chen DY, et al. Suspected multiple sclerosis: MR imaging with a thin-section fast FLAIR pulse sequence. Radiology. 1995;196:505-10.
17. Gawne-Cain ML, O'Riordan JI, Thompson AJ, Moseley IF, Miller DH. Multiple sclerosis lesion detection in the brain: a comparison of fast fluid-attenuated inversion recovery and conventional T2-weighted dual spin echo. Neurology. 1997;49:364-70.
18. Yousry TA, Filippi M, Becker C, Horsfield MA, Voltz R. Comparison of MR pulse sequences in the detection of multiple sclerosis lesions. AJNR Am J Neuroradiol. 1997;18:959-63.
19. Lycklama à Nijeholt GJ, Castelijns JA, Weerets J, et al. Sagittal MR of multiple sclerosis in the spinal cord: fast versus conventional spin-echo imaging. Am J Neuroradiol. 1998;19:355-60.
20. Lycklama G, Thompson A, Filippi M, et al. Spinal-cord MRI in multiple sclerosis. Lancet Neurol. 2003;2:555-62.
21. Kidd D, Thorpe JW, Thompson AJ, et al. Spinal cord MRI using multi-array coils and fast spin echo. II. Findings in multiple sclerosis. Neurology. 1993;43:2632-7.
22. Molyneux PD, Tubridy N, Parker GJ, et al. The effect of section thickness on MR lesion detection and quantification in multiple sclerosis. AJNR Am J Neuroradiol. 1998;19:1715-20.
23. Gawne-Cain ML, Webb S, Tofts P, Miller DH. Lesion volume measurement in multiple sclerosis: how important is accurate repositioning? J Magn Reson Imaging. 1996;6:705-13.
24. Gallagher HL, MacManus DG, Webb SL, Miller DH. A reproducible repositioning method for serial magnetic resonance imaging studies of the brain in treatment trials for multiple sclerosis. J Magn Reson Imaging. 1997;7:439-41.
25. Filippi M, Marciano N, Capra R, et al. The effect of imprecise repositioning on lesion volume measurements in patients with multiple sclerosis. Neurology. 1997;49:274-6.
26. Tan IL, Van Schijndel RA, Fazekas F, et al. Image registration and subtraction to detect active T(2) lesions in MS: an interobserver study. J Neurol. 2002;249:767-73.
27. Masdeu JC, Quinto C, Olivera C, Tenner M, Leslie D, Visintainer P. Open-ring imaging sign: highly specific for atypical brain demyelination. Neurology. 2000;54:1427-33.
28. Cotton F, Weiner HL, Jolesz FA, Guttmann CR. MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals. Neurology. 2003;60:640-6.
29. Barkhof F, Filippi M, Van Waesberghe JH, et al. Improving interobserver variation in reporting gadolinium-enhanced MRI lesions in multiple sclerosis. Neurology. 1997;49:1682-8.
30. Janardhan V, Suri S, Bakshi R. Multiple sclerosis: hyperintense lesions in the brain on nonenhanced T1-weighted MR images evidenced as areas of T1 shortening. Radiology. 2007;244:823-31.
31. Filippi M, Yousry T, Campi A, et al. Comparison of triple dose versus standard dose gadolinium-DTPA for detection of MRI enhancing lesions in patients with MS. Neurology. 1996;46:379-84.
32. Mathews VP, Caldemeyer KS, Ulmer JL, Nguyen H, Yuh WT. Effects of contrast dose, delayed imaging, and magnetization transfer saturation on gadolinium-enhanced MR imaging of brain lesions. J Magn Reson Imaging. 1997;7:14-22.
33. Sardanelli F, Iozzelli A, Losacco C, Murialdo A, Filippi M. Three subsequent single doses of gadolinium chelate for brain MR imaging in multiple sclerosis. AJNR Am J Neuroradiol. 2003;24:658-62.
34. Broome DR. Nephrogenic systemic fibrosis associated with gadolinium based contrast agents: a summary of the medical literature reporting. Eur J Radiol. 2008;66:230-4.
35. Van Walderveen MA, Barkhof F, Hommes OR, et al. Correlating MRI and clinical disease activity in multiple sclerosis: relevance of hypointense lesions on short-TR/short-TE (T1-weighted) spin-echo images. Neurology. 1995;45:1684-90.
36. Molyneux PD, Miller DH, Filippi M, et al. Visual analysis of serial T2-weighted MRI in multiple sclerosis: intra- and interobserver reproducibility. Neuroradiology. 1999;41:882-8.
37. CHAMPS Study Group. MRI predictors of early conversion to clinically definite MS in the CHAMPS placebo group. Neurology. 2002;59:998-1005.
38. Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain. 1997;120:2059-69.
39. Horowitz AL, Kaplan RD, Grewe G, White RT, Salberg LM. The ovoid lesion: a new MR observation in patients with multiple sclerosis. AJNR Am J Neuroradiol. 1989;10:303-5.
40. Bitsch A, Kuhlmann T, Stadelmann C, Lassmann H, Lucchinetti C, Bruck W. A longitudinal MRI study of histopathologically defined hypointense multiple sclerosis lesions. Ann Neurol. 2001;49:793-6.
41. Gass A, Filippi M, Rodegher ME, Schwartz A, Comi G, Hennerici MG. Characteristics of chronic MS lesions in the cerebrum, brainstem, spinal cord, and optic nerve on T1-weighted MRI. Neurology. 1998;50:548-50.
42. Seewann A, Vrenken H, Van der Valk P, et al. Diffusely abnormal white matter in chronic multiple sclerosis: imaging and histopathologic analysis. Arch Neurol. 2009;66:601-9.
43. Bedell BJ, Narayana PA. Implementation and evaluation of a new pulse sequence for rapid acquisition of double inversion recovery images for simultaneous suppression of white matter and CSF. J Magn Reson Imaging. 1998;8:544-7.
44. Geurts JJ, Pouwels PJ, Uitdehaag BM, Polman CH, Barkhof F, Castelijns JA. Intracortical lesions in multiple sclerosis: improved detection with 3D double inversion-recovery MR imaging. Radiology. 2005;236:254-60.
45. Erskine MK, Cook LL, Riddle KE, Mitchell JR, Karlik SJ. Resolution-dependent estimates of multiple sclerosis lesion loads. Can J Neurol Sci. 2005;32:205-12.
46. Sicotte NL, Voskuhl RR, Bouvier S, Klutch R, Cohen MS, Mazziotta JC. Comparison of multiple sclerosis lesions at 1.5 and 3.0 Tesla. Invest Radiol. 2003;38:423-7.
47. Wattjes MP, Harzheim M, Kuhl CK, et al. Does high-field MR imaging have an influence on the classification of patients with clinically isolated syndromes according to current diagnostic MR imaging criteria for multiple sclerosis? AJNR Am J Neuroradiol. 2006;27:1794-8.
48. Schmitz BL, Aschoff AJ, Hoffmann MH, Grön G. Advantages and pitfalls in 3T MR brain imaging: a pictorial review. AJNR Am J Neuroradiol. 2005;26:2229-37.
49. Miller DH. Biomarkers and surrogate outcomes in neurodegenerative disease: lessons from multiple sclerosis. NeuroRx. 2004;1:284-94.
50. Bakshi R, Minagar A, Jaisani Z, Wolinsky JS. Imaging of multiple sclerosis: role in neurotherapeutics. NeuroRx. 2005;2:277-303.
51. Zivadinov R, Stosic M, Cox JL, Ramasamy DP, Dwyer MG. The place of conventional MRI and newly emerging MRI techniques in monitoring different aspects of treatment outcome. J Neurol. 2008;255(Suppl 1):61-74.
52. Law M, Meltzer DE, Cha S. Spectroscopic magnetic resonance imaging of a tumefactive demyelinating lesion. Neuroradiology. 2002;44:986-9.
53. Ernst T, Chang L, Walot I, Huff K. Physiologic MRI of a tumefactive multiple sclerosis lesion. Neurology. 1998;51:1486-8.
54. De Stefano N, Caramanos Z, Preul MC, Francis G, Antel JP, Arnold DL. In vivo differentiation of astrocytic brain tumors and isolated demyelinating lesions of the type seen in multiple sclerosis using 1H magnetic resonance spectroscopic imaging. Ann Neurol. 1998;44:273-8.

55. De Stefano N, Bartolozzi ML, Guidi L, Stromillo ML, Federico A. Magnetic resonance spectroscopy as a measure of brain damage in multiple sclerosis. J Neurol Sci. 2005;233:203-8.
56. Majós C, Aguilera C, Alonso J, et al. Proton MR spectroscopy improves discrimination between tumor and pseudotumoral lesion in solid brain masses. AJNR Am J Neuroradiol. 2009;30:544-51.
57. De Stefano N, Filippi M, Miller D, et al. Guidelines for using proton MR spectroscopy in multicenter clinical MS studies. Neurology. 2007;69:1942-52.
58. Simon JH. Brain atrophy in multiple sclerosis: what we know and would like to know. Mult Scler. 2006;12:679-87.
59. Bermel RA, Bakshi R. The measurement and clinical relevance of brain atrophy in multiple sclerosis. Lancet Neurol. 2006;5:158-70.
60. Fisher E, Lee JC, Nakamura K, Rudick RA. Gray matter atrophy in multiple sclerosis: a longitudinal study. Ann Neurol. 2008;64:255-65.
61. Rudick RA, Lee JC, Nakamura K, Fisher E. Gray matter atrophy correlates with MS disability progression measured with MSFC but not EDSS. J Neurol Sci. 2009;282(1-2):.
62. Chard DT, Griffin CM, Parker GJ, et al. Brain atrophy in clinically early relapsing-remitting multiple sclerosis. Brain. 2002; 125:327-37.
63. Rudick RA, Fisher E, Lee JC, Simon J, Jacobs L, Multiple Sclerosis Collaborative Research Group. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Neurology. 1999;53:1698-704.
64. Miller DH, Barkhof F, Frank JA, Parker GJ, Thompson AJ. Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. Brain. 2002;125:1676-95.
65. Losseff NA, Webb SL, O'Riordan JI, et al. Spinal cord atrophy and disability in multiple sclerosis. A new reproducible and sensitive MRI method with potential to monitor disease progression. Brain. 1996;119:701-8.
66. Rovira A, Alonso J, Cucurella G, et al. Evolution of multiple sclerosis lesions on serial contrast-enhanced T1-weighted and magnetization-transfer MR images. AJNR Am J Neuroradiol. 1999;20:1939-45.
67. Horsfield MA. Magnetization transfer imaging in multiple sclerosis. J Neuroimaging. 2005;15:58S-67S.
68. Oreja-Guevara C, Charyl A, Caputo D, Cavarretta R, Sormani MP, Filippi M. Magnetization transfer magnetic resonance imaging and clinical changes in patients with relapsing-remitting multiple sclerosis. Arch Neurol. 2006;63: 736-40.
69. Chen JT, Collins DL, Atkins HL, et al. Magnetization transfer ratio evolution with demyelination and remyelination in multiple sclerosis lesions. Ann Neurol. 2008;63:254-62.
70. Giacomini PS, Levesque IR, Ribeiro L, et al. Measuring demyelination and remyelination in acute multiple sclerosis lesion voxels. Arch Neurol. 2009;66:375-81.
71. Rovaris M, Gass A, Bammer R, et al. Diffusion MRI in multiple sclerosis. Neurology. 2005;65:1526-32.
72. Oreja-Guevara C, Rovaris M, Iannucci G, Valvasina P, Caputo D, Cavarretta R, et al. Progressive grey matter damage in patients with relapsing-remitting MS: A longitudinal diffusion tensor MRI study. Arch Neurol. 2005;62:578-84.
73. Renoux J, Facon D, Fillard P, et al. MR diffusion tensor imaging and fiber tracking in inflammatory diseases of the spinal cord. AJNR Am J Neuroradiol. 2006;27:1947-51.
74. Pantano P, Mainero C, Caramia F. Functional brain reorganization in multiple sclerosis: evidence from fMRI studies. J Neuroimaging. 2006;16:104-14.
75. Mainero C, Inghilleri M, Pantano P, et al. Enhanced brain motor activity in patients with MS after a single dose of 3,4-diaminopyridine. Neurology. 2004;62:2044-50.