Effective Utilization of MRI in the Diagnosis and Management of Multiple Sclerosis

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KEYWORDS

• MRI • Multiple sclerosis • Disease-modifying treatment • Diagnosis • Management • Lesions • Atrophy • Standardized MRI protocol

KEY POINTS

- MRI is the most important tool for diagnosis and management of patients with multiple sclerosis (MS).
- MRI is able to detect white matter (WM) lesions in the central nervous system and their dissemination in space and time.
- MRI is used for tracking disease activity and for prognostic evaluation, as well for monitoring treatment efficacy and safety.
- Nonconventional and quantitative MRI measures can capture features of MS histopathologic findings beyond WM lesions but, for various reasons, are not currently implemented in clinical practice.
- Consensus guidelines on standardized MRI acquisition protocol have been recently published.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating and degenerative disease of the central nervous system (CNS), leading to a wide range of disability. The diagnosis of MS relies on the McDonald criteria, revised in 2010,[1] which is based on the evaluation of clinical symptoms (at presentation with clinically isolated syndrome [CIS] and/or in the history) and MRI of the CNS. The relevance of MRI as a noninvasive tool for the initial investigation of suspected MS and for disease monitoring over time has constantly grown due to the widespread availability of magnetic resonance (MR) scanners, advances in computational technology, and a plethora of scientific studies.

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In recent years, several disease-modifying treatments (DMTs), acting with different mechanisms, have become available for MS. In particular, DMTs can decrease the focal inflammatory activity; the rate of brain atrophy; and, ultimately, the accrual of disability. It is important to choose for each patient the most adequate DMT and to monitor its efficacy and possible adverse effects over time.

USE OF MRI IN THE DIAGNOSIS OF MULTIPLE SCLEROSIS

Over the past 20 years, the neurologic community has adopted for MS various diagnostic criteria, which have been regularly modified as new lines of evidence and expert recommendations have emerged. The latest criteria were established in 2010 by an international panel and consist of a revision of the classic McDonald criteria.[1] The diagnostic criteria for MS have shown their validity and reliability when applied to patients younger than age 50 years with a typical clinical syndrome consistent with demyelination of the CNS (ie, CIS), such as optic neuritis, transverse myelitis, and brainstem syndromes, and after exclusion of alternative conditions mimicking MS.

MRI is currently the most relevant tool for MS diagnosis and is formally included in the diagnostic workup of patients with CIS suggestive of MS. Indeed, it shows high sensitivity for detection of focal white matter (WM) lesions in the CNS and specificity for lesion dissemination in space (DIS) and dissemination in time (DIT). In particular, DIS is fulfilled by the presence of 1 or more lesions in 2 of 4 characteristic anatomic locations (periventricular, juxtacortical, infratentorial, or spinal cord). DIT is demonstrated by simultaneous presence of gadolinium (Gd)-enhancing and Gd-nonenhancing lesions, thus indicating at least 2 demyelinating events, or by new T2 and/or Gd-enhancing lesion at follow-up MR examination. For the first time, the latest criteria allow an MS diagnosis based on a single MRI scan showing both DIS and DIT.

Sizes, shapes, and locations of MS lesions are variable. However, typically, they have an ovoid shape, a diameter greater than or equal to 3 mm, and cluster close to the ventricles and in the corpus callosum, although juxtacortical and infratentorial regions are other common sites of involvement. On sagittal images, lesions can appear as “fingers” stemming from the ventricular borders and reaching the corona radiata. A well-defined nodular enhancement usually occurs in acute small lesions, whereas a ring-like appearance may be present in subacute large lesions, which have a higher level of tissue destruction and, therefore, tend to resolve more slowly.

Importantly, the diagnostic work-up may be inconclusive in early MS, thus clinical and MRI follow-up may be needed to confirm the diagnosis. A 3 to 6 month interval between the baseline and follow-up MR examination has been recommended and, in the case in which no DIT occurs at that time, a further scan is recommended 6 to 12 months later.[2] If the brain MRI is normal over time, the diagnosis of MS appears less likely.

MRI is also able to detect incidental lesions suggestive of MS histopathologic findings in the brain and spinal cord of subjects without past or current neurologic symptoms. This condition has been termed radiologically isolated syndrome.[3] A new consensus article by the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) network provides recommendations useful for a proper stratification and management of these patients, which distinguishes between those at high risk for developing MS and those who have a low risk and thus are improperly exposed to unnecessary medical testing and treatment.[4]

The 2010 revisions of the McDonald criteria have received some criticism regarding their leniency, possibly leading to false-positive diagnosis, and the lack of consideration of MS pathologic findings beyond WM lesions. Against this background, there

is a need for additional MRI measures to help differentiate among lesions of different pathogenesis. The demonstration of the "central vein sign", based on the perivascular location of MS lesions, and increased iron deposition help differentiate MS lesions from lesions of ischemic small vessel disease or neuromyelitis optica. These findings are particularly visible at high MR field strengths ($\geq$3.0 T) and when using specific sequences, such as susceptibility-weighted imaging and a special type of fluid attenuated inversion recovery (FLAIR*).[5,6]

Pathologic gray matter (GM) is present in MS brain and has a clear-cut clinical relevance, especially for cognitive impairment.[7] Indeed, cortical lesions (CLs) turn out to be rather specific for MS and their incorporation into diagnostic criteria would further increase their specificity.[8] Relatively novel MR sequences, such as double inversion recovery and phase-sensitive inversion recovery, have increased the detection rate of CLs and the sensitivity can be even further improved by using high MR field strengths.[9,10] Despite these advantages, CLs have not yet been incorporated into the McDonald diagnostic criteria and are not used as an imaging endpoint for treatment trials. Indeed, there is currently a lack of standardized image acquisition and analysis for CLs and, even using a dedicated protocol, the MRI sensitivity is much lower than histopathology.[11]

USE OF MRI IN THE MANAGEMENT OF MULTIPLE SCLEROSIS

Alongside its fundamental role for MS diagnosis, MRI is used for tracking subclinical disease activity, for prognostic evaluation, and for monitoring treatment effect, thus providing important pieces of information for ongoing patient management.

MRI for Monitoring Disease Activity

A high WM lesion load or the occurrence of lesions in a particular location (eg, brainstem) at the time of MS diagnosis predicts the development of future clinical disability in the medium to long term.[12,13] Although a cutoff for lesion count is debatable, patients with CIS showing greater than 10 T2 lesions have a significantly higher risk for long-term (eg, 20 years) disability progression compared with those patients having less than 4 T2 lesions.[14] It is well known that disease activity as measured by MRI is more sensitive than the frequency of clinical relapses. For this reason, serial MRI examinations are a reliable tool for detection and tracking subclinical disease activity. The occurrence of new lesions during the first 5 years of disease is associated with worse long-term (ie, 20 years) prognosis, even in presence of low lesion count.[14]

The most commonly used MRI measures of disease activity in clinical practice are the active lesions, characterized by Gd-enhancing T1 lesions, new or enlarging T2 lesions in serial MR scans, and the disease burden, which is based on the total T2 lesion volume. Although Gd-enhancing lesions are a reliable measure of acute inflammation with blood-brain barrier breakdown, their enhancement is transient, typically lasting about 6 to 8 weeks, thus monitoring disease activity by this method would require MRI acquisitions more frequently than is normally feasible in clinical practice (eg, monthly rather than annually or semiannually). For this reason, monitoring changes of T2 lesion number and volume currently remains the most practical measure of disease activity over time.

Another lesional MRI measure is characterized by hypointense T1 lesions (so-called "black holes"), which reflect old and inactive lesions associated with severe tissue damage (demyelination and, especially, axonal loss). Their count may be low in the early disease course and they are not suitable for monitoring disease activity.

Moreover, they showed no independent role for predicting conversion of CIS to clinically definite MS.[15]

MRI for Treatment Response

Lesion measures

As for any chronic disease, monitoring treatment in MS is necessary to achieve favorable long-term outcomes. The aims of DMTs in MS are reduction of disease activity, in terms of relapse frequency and new MRI lesions, and prevention of disability worsening over time. Clinical trials investigating the efficacy of DMTs in MS include standard MRI measures, such as active MRI lesions as secondary outcome measure. A recent meta-analysis has demonstrated that treatment effect on relapses until 2 years is predicted by the effect on active MS lesions within 6 to 9 months.[16]

It is common in clinical practice to start a DMT and then monitor its efficacy using follow-up MRI examinations. Indeed, MRI activity occurs with a frequency 5 to 10 times higher than clinical activity in relapsing-remitting MS (RRMS), thus providing a sensitive measure of disease activity and treatment efficacy. Several studies have evaluated the role of lesional MRI measures obtained early in the course of a DMT, such as interferon (IFN) β, and risk for disease worsening in the long term. The most predictive measures in this context include 2 to 5 new T2 lesions in the first 1 to 2 years of treatment.[17] Detection or absence of disease activity by MRI in a patient receiving a DMT represents a measure of treatment response. This implies that before the initiation or the switch of a treatment, a baseline and a follow-up MRI examination are needed. However, due to different mechanisms of action and time to treatment response of the various DMTs in MS, some investigators suggested that the reference scan should be obtained 3 to 6 months after treatment initiation or switch. Further MRI scans useful to monitor subclinical MS activity in RRMS should be obtained at intervals of 6 to 12 months, depending on the level of disease activity. A less frequent monitoring would be more suitable for patients who have been clinically stable for several years or who have a progressive disease without evidence of disease activity on previous assessments.

The evaluation of longitudinal MR examinations in clinical practice can be difficult because images are acquired with different scanners and acquisition parameters. In this context, detection of Gd lesions is a simple task for clinicians, whereas help from MRI experts is warranted for detection of new or enlarging T2 lesions.

Studies from other chronic autoimmune diseases (eg, rheumatologic) suggest that defining an explicit treatment target for close disease monitoring may have significant benefit on long-term outcome.[18] In the context of MS, it was recently proposed to use the so-called no evidence of disease activity (NEDA), which is conventionally defined as no relapses, no active MRI lesions (new T2 or Gd lesions), and no new disability accumulation, typically measured using the Expanded Disability Status Scale.[19] Based on this definition, assessment of NEDA status relies heavily on MRI monitoring. Recent studies on real-world cohorts of RRMS patients showed that NEDA can be found in the long term (7–10 years) in a minimal proportion of cases (8%–9%) and is even more difficult to sustain when a potential marker of neurodegeneration, such as brain atrophy, is included in the definition.[20,21] It is currently unknown whether the NEDA concept can be extended to treatments different from IFN.

Nonconventional measures

In clinical practice, widespread changes (ie, neurodegeneration or possible remyelination) in the normal-appearing WM and GM beyond WM lesions cannot be assessed

adequately by conventional MRI (eg, T2-weighted and post-Gd T1 sequences) but need the application of nonconventional MRI measures and techniques.

Brain atrophy In the last decade or so, several studies have demonstrated that brain volume reduction (atrophy), which is a measure of neurodegeneration, occurs even in the earliest MS stages. The clinical relevance of brain atrophy, especially of the GM, stems from a better association, compared with WM lesion measures, with clinical progression, in terms of both disability and cognitive impairment.[22] Both GM compartments, the cortex and deep GM (especially thalamus), are affected.

Pathogenesis of brain atrophy in MS is complex and not completely clear.[7] It is mostly driven by GM atrophy, which may be a primary process[23] or may be secondary to axonal transection by WM lesions.[24,25] However, recent studies showed that the relationship of GM atrophy with WM focal pathologic findings may depend on the anatomic region considered (eg, motor cortex thinning related to corticospinal tract damage)[26] and on the disease course, with cortical atrophy more related to normal-appearing WM in longstanding RRMS.[27]

Being a measure of neurodegeneration, preventing brain atrophy will surely lead to relevant clinical benefit. MRI brain volume measures have been used in several clinical trials as outcome measure to assess the effect of DMT. A recent meta-analysis performed at the trial level demonstrated that treatment effect on brain atrophy correlates with treatment effect on disability.[28] Against this background, brain atrophy should ideally become a primary outcome measure in clinical trials. However, it should be taken into account that during the first 6 months to 1 year of DMT use, brain volume may decrease due to the treatment-related resolution of ongoing WM inflammation and edema ("pseudoatrophy").[29]

Although proposed by different groups, no standardized protocol for atrophy measurement is available and, for this reason, this measure is not currently implemented in clinical practice for routine assessment of single MS patients.

Remyelination Several remyelinating treatments are currently under investigation in phase 1 and 2 clinical trials.[30,31] Conventional MRI measures are of limited value in monitoring remyelination, although a recent randomized trial with IFN β-1b in CIS demonstrated a reduction of black holes.[32] Various advanced MRI techniques exist for a more specific in vivo assessment of the myelin content, including magnetization transfer (MT) imaging and diffusion tensor imaging, which would be the most feasible techniques in a clinical setting, and positron emission tomography. In particular, significant changes in MT ratio, consistent with demyelination and remyelination, and following different temporal evolution, were found in different regions of MS lesions for at least 3 years after formation.[33] Although the use of quantitative MRI measures for the assessment of remyelination has some potential, clinicians should consider that effective utilization of these measures in clinical practice and in multicenter studies is prevented with respect to conventional MRI by various factors, including longer scan time, complex postprocessing analyses, and lack of standardization.

Monitoring treatment adverse effects

Since the approval of the novel and potent DMT for MS, the need for monitoring potential adverse effects has increased.[34] In particular, brain MRI has been used for monitoring MS patients treated with natalizumab (NTZ), a recombinant humanized monoclonal antibody.[35] Progressive multifocal leukoencephalopathy (PML) is a relatively rare but serious opportunistic infection caused by reactivation of the John Cunningham (JC) virus during NTZ treatment; brain MRI represents the most valuable

screening tool for its early detection, even at asymptomatic stage.[36] Guidelines for MRI screening in NTZ-treated patients have been recently published.[2] Brain MRI, including FLAIR, T2-weighted, and diffusion-weighted imaging sequences, is recommended every 3 to 4 months in patients at high risk (ie, JC virus seropositive, treatment duration $\geq$18 months) and once a year in patients at low risk of PML (ie, JC virus seronegative). However, clinicians should consider that MRI-based monitoring for early PML detection is not limited only to patients treated with NTZ, but it should be extended to patients treated with other DMTs, such as alemtuzumab, rituximab, or dimethylfumarate.[34]

STANDARDIZED MRI PROTOCOL

Despite the routine use of MRI in the diagnosis and management of MS patients, there is currently no evidence defining its optimal use. It is well known that several MRI acquisition parameters (eg, field strength, sequence, spatial resolution, coil type) can influence the detection of focal MS histopathologic findings, especially in a multicenter setting. Thus, it is widely accepted that standardized MRI protocols are urgently needed. However, even in the 2010 revision of the McDonald criteria, specific suggestions for MRI acquisition are lacking. In this respect, the MAGNIMS network has recently published European consensus guidelines.[2,37]

Brain MRI should be performed at least on a 1.5-T scanner but a 3 T scanner is recommended for the better sensitivity to MS lesions due to improved image resolution and signal-to-noise ratio, although this does not seem to allow an earlier MS diagnosis.[38] The spatial resolution should be 1×1 mm in-plane and 3-mm slice thickness (voxel size: $1\times1\times3$ mm). Proton-density (PD) and T2-weighted sequences are considered the reference for detection of hyperintense (ie, bright) WM lesions. FLAIR sequence is useful for excluding cerebrospinal fluid (CSF)-filled enlarged Virchow–Robin spaces and it shows a higher sensitivity for juxtacortical and periventricular lesions but lower sensitivity for those lesions in the infratentorial area. High-resolution (3-dimensional, voxel size: 1 mm^3) FLAIR is ideally preferred due to higher contrast-to-noise ratio, availability of multiplanar reconstructions, and registration of longitudinal images.

A standard T1-weighted spin echo sequence can show chronic T1 hypointense lesions ("black holes"), reflecting irreversible tissue damage, and macroscopic atrophy. Gd should be administered before the acquisition of PD, T2 or FLAIR sequences to allow longer circulation time and better detection of acute lesions.

Spinal cord MRI is relevant for MS diagnosis, but it may be less sensitive for assessing subclinical disease activity and thus for disease management. It is more demanding than brain MRI due to small tissue volume, occurrence of various artifacts (eg, CSF flow and blood vessel pulsations), harder detection of MS lesions, and prolonged scan time. Spinal MRI images should be acquired on a scanner with at least 1.5-T field strength and, unlike brain MRI, no evidence exists that 3 T scanners have higher sensitivity for lesion detection. For spinal cord, the standard sequence for MS is considered dual-echo (PD and T2-weighted) with at least $1\times1\times3$ mm spatial resolution and sagittal orientation. Indeed, in this case, FLAIR lacks sensitivity for spinal lesions. Alternatively, short-tau inversion recovery T2-weighted sequence may be used in presence of flow-related artifacts, which may lead to false-positive results. The role of Gd administration in spinal cord MRI is still unclear because, compared with brain lesions, only a small proportion of spinal lesions show enhancement and, when it occurs, it is commonly associated with neurologic symptoms.[39]

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