2021 MAGNIMS–CMSC–NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis

*Mike P Wattjes, Olga Ciccarelli, Daniel S Reich, Brenda Banwell, Nicola de Stefano, Christian Enzinger, Franz Fazekas, Massimo Filippi, Jette Frederiksen, Claudio Gasperini, Yael Hacohen, Ludwig Kappos, David K B Li, Kshitij Mankad, Xavier Montalban, Scott D Newsome, Jiwon Oh, Jacqueline Palace, Maria A Rocca, Jaume Sastre-Garriga, Mar Tintoré, Anthony Traboulsee, Hugo Vrenken, Tarek Yousry, Frederik Barkhof, Àlex Rovira on behalf of the Magnetic Resonance Imaging in Multiple Sclerosis study group, the Consortium of Multiple Sclerosis Centres, and North American Imaging in Multiple Sclerosis Cooperative MRI guidelines working group**

The 2015 Magnetic Resonance Imaging in Multiple Sclerosis and 2016 Consortium of Multiple Sclerosis Centres guidelines on the use of MRI in diagnosis and monitoring of multiple sclerosis made an important step towards appropriate use of MRI in routine clinical practice. Since their promulgation, there have been substantial relevant advances in knowledge, including the 2017 revisions of the McDonald diagnostic criteria, renewed safety concerns regarding intravenous gadolinium-based contrast agents, and the value of spinal cord MRI for diagnostic, prognostic, and monitoring purposes. These developments suggest a changing role of MRI for the management of patients with multiple sclerosis. This 2021 revision of the previous guidelines on MRI use for patients with multiple sclerosis merges recommendations from the Magnetic Resonance Imaging in Multiple Sclerosis study group, Consortium of Multiple Sclerosis Centres, and North American Imaging in Multiple Sclerosis Cooperative, and translates research findings into clinical practice to improve the use of MRI for diagnosis, prognosis, and monitoring of individuals with multiple sclerosis. We recommend changes in MRI acquisition protocols, such as emphasising the value of three dimensional-fluid-attenuated inversion recovery as the core brain pulse sequence to improve diagnostic accuracy and ability to identify new lesions to monitor treatment effectiveness, and we provide recommendations for the judicious use of gadolinium-based contrast agents for specific clinical purposes. Additionally, we extend the recommendations to the use of MRI in patients with multiple sclerosis in childhood, during pregnancy, and in the post-partum period. Finally, we discuss promising MRI approaches that might deserve introduction into clinical practice in the near future.

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*Members are listed in the appendix

Department of Diagnostic and Interventional Neuroradiology, Hannover Medical School, Hannover, Germany (Prof M P Wattjes MD); **Department of Radiology and Nuclear Medicine, Amsterdam UMC, Amsterdam, Netherlands** (Prof M P Wattjes, H Vrenken PhD, Prof F Barkhof MD); **Lysholm Department of Neuroradiology, UCLH National Hospital for Neurology and Neurosurgery, London, UK** (Prof T Yousry MD); **Neuroradiological Academic Unit** (Prof T Yousry) **and Faculty of Brain Sciences** (Prof O Ciccarelli MD, Y Hacohen MD, Prof F Barkhof), **University College London Queen Square Institute of Neurology, University College London, London, UK; National Institute for Health Research University College London Hospitals Biomedical Research Centre, London, UK** (Prof O Ciccarelli, Prof F Barkhof); **Translational Neuroradiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA** (D S Reich MD); **Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA** (Prof B Banwell MD); **Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA** (Prof B Banwell); **Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy** (Prof N de Stefano MD); **Department of Neurology**

Introduction

The value of MRI in patients with multiple sclerosis for diagnostic, prognostic, and monitoring purposes is well established and its implementation has been specified in several consensus and guideline papers that vary slightly between North America, Europe, and the Middle East. Universal adoption of a standardised approach to MRI in clinical practice, including image acquisition protocols and timing of scans, is a major challenge because of differences in health-care systems and clinical practices between countries. The 2015 Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS)[1,2] and 2016 Consortium of Multiple Sclerosis Centres (CMSC)[3] consensus guidelines on the use of MRI in patients for diagnosis, prognosis, and monitoring of multiple sclerosis guided neuroradiologists and neurologists to standardise their image acquisition protocols and the indications for when and how to use MRI, prompting international and national societies to establish similar recommendations.[4,5]

Since the publication of those guidelines, new developments and scientific data have led to considerable advances in knowledge. These include the 2017 revisions of the McDonald criteria,[6] evolving safety concerns about the repetitive administration of intravenous gadolinium-based contrast agents (GBCAs) due to the potential risk of gadolinium accumulation in the brain,[7,8] and emerging evidence regarding the role of spinal cord MRI for prognosis and monitoring of patients with multiple sclerosis. These and other new developments in the use of MRI in patients with multiple sclerosis prompted us to begin a critical review of the literature, revision of the 2015 MAGNIMS consensus guidelines, and harmonisation of these recommendations with a new revision of the 2016 CMSC guidelines and incorporation of the viewpoints of the North American Imaging in Multiple Sclerosis Cooperative (NAIMS).

These 2021 MAGNIMS–CMSC–NAIMS international consensus recommendations on MRI in patients with multiple sclerosis provide updated guidance on how and when to use MRI for diagnosis, prognosis, and treatment monitoring of multiple sclerosis, with special focus on the use of standardised MRI protocols, the judicious use of GBCAs, and standardised reporting. Additionally, we extend the recommendations to the use of MRI in special populations and situations, such as patients with multiple sclerosis during childhood, pregnancy, and the post-partum period. Finally, we discuss new and promising MRI techniques that might become clinically relevant in the near future.

Methods

A MAGNIMS panel of experts in the diagnosis and management of patients with multiple sclerosis convened in Graz, Austria, on April 12–13, 2019. The panel discussed and agreed on new or modified recommendations on the use of brain and spinal cord MRI in clinical practice. A second panel of experts convened independently in Newark, NJ, USA, on Oct 25, 2019, including members of the CMSC and the NAIMS. Following discussion among the chairs of the MAGNIMS, NAIMS, and CMSC Working

(Prof C Enzinger MD, Prof F Fazekas MD) **and Division of Neuroradiology, Vascular and Interventional Radiology, Department of Radiology** (Prof C Enzinger), **Medical University of Graz, Graz, Austria; Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience** (Prof M Filippi MD, Prof M A Rocca MD), **Neurology Unit** (Prof M Filippi, Prof M A Rocca), **and Neurophysiology Unit** (Prof M Filippi), **IRCCS San Raffaele Scientific Institute, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy** (Prof M Filippi, Prof M A Rocca); **Department of Neurology, Rigshospitalet Glostrup, University Hospital of Copenhagen, Glostrup, Denmark** (Prof J Frederiksen MD); **Department of Neurology, San Camillo-Forlanini Hospital, Roma, Italy** (Prof C Gasperini MD); **Department of Paediatric Neurology** (Y Hacohen) **and Department of Neuroradiology** (K Mankad MD), **Great Ormond Street Hospital for Children, London, UK; Department of Neurology and Research Center for Clinical Neuroimmunology and Neuroscience, University Hospital of Basel and University of Basel, Basel, Switzerland** (Prof L Kappos MD); **Department of Radiology** (D K B Li MD) **and Division of Neurology** (Prof A Traboulsee MD), **University of British Columbia, Vancouver, BC, Canada; Multiple Sclerosis Centre of Catalonia, Department of Neurology–Neuroimmunology** (Prof X Montalban MD, J Sastre-Garriga MD, M Tintoré MD) **and Section of Neuroradiology, Department of Radiology** (Prof À Rovira MD), **Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain; Division of Neurology, St Michael's Hospital, University of Toronto, Toronto, ON, Canada** (Prof X Montalban, J Oh MD); **Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA** (S D Newsome DO); **Nuffield Department of Clinical Neurosciences, Oxford, UK** (Prof J Palace MD)

Groups, representatives of the NAIMS and CMSC groups reviewed and revised the MAGNIMS recommendations, after which a final consensus agreement was endorsed by all groups' members. Details of the consortia, working groups, and development of the recommendations are presented in the appendix (pp 1–2).

Multiple sclerosis diagnosis

The 2017 revisions of the McDonald criteria on multiple sclerosis diagnosis[6] reinforced the importance of brain and spinal cord MRI examinations, in addition to the clinical presentation (ie, a clinical event that is suggestive of a first attack of multiple sclerosis or disability progression that is suggestive of primary progressive multiple sclerosis) and CSF analysis (ie, showing oligoclonal bands) under some circumstances.[6,9] The 2017 revisions also emphasised the strong need for strict standardisation of MRI acquisition and interpretation to avoid misdiagnosis.[6,10,11] The crucial need for a standardised brain and spinal cord MRI acquisition and reporting (appendix pp 4–6) at the time of the first clinical presentation and during the early course of multiple sclerosis goes beyond diagnostic purposes since it provides important prognostic information (appendix pp 3–4).[12,13]

Standardised brain MRI protocol for multiple sclerosis diagnosis

The 2015 MAGNIMS and 2016 CMSC guidelines recommended the use of axial single (eg, late echo) T2-weighted sequences, dual echo T2-weighted (ie, turbo or fast) spin echo sequences, axial and sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR), and contrast enhanced axial T1-weighted sequences, preferably at 3 T.[1,3] The 2017 revisions of the McDonald diagnostic criteria do not require substantial changes to this standardised protocol. However, three dimensional (3D) acquisition techniques (particularly for FLAIR and T1-weighted sequences) are now preferred to two dimensional (2D) acquisitions, as 3D techniques have become more routinely available on clinical scanners than before and they improve both lesion detection and the realignment of anatomic orientation that is necessary to detect new lesions when comparing serial MRI scans (tables 1, 2; panel 1; figure 1).[14] On the basis of its high sensitivity, sagittal 3D FLAIR acquisition is considered to be the core sequence for multiple sclerosis diagnosis and monitoring (as discussed later). However, in centres that are unable to acquire sufficiently high quality 3D FLAIR images, high quality two dimensional (2D) pulse-sequences (ie, ≤3 mm slice thickness and no gap between slices) can provide an acceptable alternative. Precontrast T1-weighted sequences are not routinely needed because precontrast images rarely assist with interpretation of postcontrast hyperintensities.

Even though 3 T scanners provide a higher detection rate for multiple sclerosis lesions and offer potentially shorter acquisition times compared with lower magnetic field strengths, there is no evidence that 3 T MRI leads to an earlier diagnosis of multiple sclerosis.[15,16] The use of 1·5 T scanners continues to be sufficient for detection of brain lesions at the time of diagnosis, as long as scans are of good quality with adequate signal-to-noise ratio and spatial resolution (ie, ≤1 mm×1 mm pixel in-plane resolution). The use of scanners with field strengths that are less than 1·5 T is not recommended (table 1, panel 1).

Ultra-high-field MRI operating at 7 T has been used for research purposes and has added value for the detection of cortical grey matter lesions.[17–19] However, 7 T systems are not widely available and are mostly used for research. Additionally, image interpretation can be challenging due to substantial influence of the magnetic field strength on tissue relaxation time, leading to changes in tissue contrast. Therefore, image acquisition and interpretation for clinical routine purposes require dedicated expertise and the use of 7 T in clinical practice is not recommended at this stage (panel 1).

The recognition of gadolinium deposition in the CNS has led to specific recommendations on its use by the European Medicines Agency and the US Food and Drug Administration.[7,8] However, the use of GBCAs continues to be invaluable during the initial investigation of multiple sclerosis to show dissemination in time (DIT) and to

	Brain	Spinal cord	Optic nerve
Field strength	≥1·5 T (preferably 3 T)	≥1·5 T (3 T has no added value compared with 1·5 T)	≥1·5 T
Slice thickness	For 3D imaging, 1 mm isotropic is preferred but, if over contiguous (through plane and in plane), not >1·5 mm, with 0·75 mm overlap; for 2D imaging, ≤3 mm with no gap (except for diffusion-weighted imaging, for which the slice thickness should be ≤5 mm with a 10–30% gap)	Sagittal slices should be ≤3 mm with no gap; axial slices should be ≤5 mm with no gap	≤2–3 mm with no gap
In-plane resolution	≤1 mm × 1 mm	≤1 mm × 1 mm	≤1 mm × 1 mm
Coverage	Whole brain (include as much of cervical cord as possible)	Cervical and thoracolumbar spinal cord, to include conus	Optic nerve and optic chiasm
Axial scan orientation	Subcallosal plane to prescribe (ie, for 2D imaging) or reformat (ie, for 3D imaging) axial oblique slices	Perpendicular to the sagittal axis of the spinal cord	Aligned to the orientation of the optic nerve and optic chiasm

3D=three dimensional. 2D=two dimensional.

Table 1: **Basic MRI parameters**

	Multiple sclerosis diagnosis	Assessment of disease activity and monitoring effectiveness of the disease-modifying treatment*	Safety monitoring for disease-modifying treatment (eg, progressive multifocal leukoencephalopathy screening)
Brain MRI protocol			
Axial T2-weighted (TSE or FSE) sequences†	Recommended	Recommended (optional if high-quality sagittal 3D T2-weighted FLAIR and multiplanar reconstruction in axial and sagittal planes are available)	Recommended (optional if high-quality sagittal 3D T2-weighted FLAIR and multiplanar reconstruction in axial and sagittal planes are available)
Sagittal T2-weighted FLAIR (preferably 3D; fat suppression is optional)	Recommended	Recommended	Recommended
Axial T2-weighted FLAIR (unnecessary if a sagittal 3D FLAIR with multiplanar reconstruction is obtained; fat suppression is optional)	Recommended	Recommended	Recommended
Axial (or 3D sagittal) T1-weighted sequences after contrast‡	Recommended	Optional	Optional
Diffusion-weighted imaging	Optional	Optional (should be considered for differential diagnosis)	Recommended
Double inversion recovery or PSIR for detecting cortical or juxtacortical lesions	Optional	Optional	Optional
High-resolution T1-weighted sequences (isotropic 3D acquisition; for quantitative assessment of brain volume)	Optional	Optional	Not required
Susceptibility-weighted imaging	Optional for assessing the central vein sign	Not required	Not required
Optic nerve MRI protocol			
Axial and coronal fat-suppressed T2-weighted sequences or STIR of optic nerve	Optional (can be considered in some clinical situations; 2D or 3D acquisition)	Not required	Not required
Axial and coronal fat-suppressed T1-weighted sequences post contrast of optic nerve	Optional (can be considered in some clinical situations; 2D or 3D acquisition)	Not required	Not required
Spinal cord MRI protocol			
At least two of: sagittal T2-weighted sequences (TSE or FSE), proton density-weighted sequences (TSE or FSE), or STIR	Recommended	Optional	Not required
Sagittal 3D heavily T1-weighted sequences (PSIR or magnetisation-prepared rapid acquisition of gradient echoes§) only for the cervical segment	Optional	Optional	Not required
Axial T2-weighted (TSE or FSE) or gradient-recalled echo to corroborate, characterise, and confirm lesions detected on sagittal images or to detect lesions in spinal cord segments with high clinical suspicions of involvement	Optional	Optional	Not required
Sagittal T1-weighted sequences (TSE or FSE) before contrast	Optional	Optional	Not required
Sagittal T1-weighted sequences (TSE or FSE) after contrast‡	Recommended	Optional	Not required
Axial T1-weighted sequences (TSE or FSE) after contrast‡	Optional	Optional	Not required

TSE=turbo spin echo. FSE=fast spin echo. FLAIR=fluid attenuated inversion recovery. PSIR=phase-sensitive inversion recovery. STIR=short tau inversion recovery. *Spinal cord MRI for assessing treatment efficacy and monitoring disease activity is not recommended on a regular basis but is advised for special clinical conditions only. †A dual echo (proton density-weighted and T2-weighted) sequence can be considered as an alternative to a single echo T2-weighted sequence. ‡Standard doses of 0·1 mmol/kg bodyweight, macrocyclic gadolinium chelates only, with a minimum delay of 5–10 min. §One of these sequences could replace T2-weighted sequences, proton density-weighted sequences, or short tau inversion recovery.

Table 2: **Standardised brain, optic nerve, and spinal MRI protocols**

exclude alternative diagnoses.[6,10] Despite previous findings that double-dose (ie, 0·2 mmol/kg body weight) and triple-dose (ie, 0·3 mmol/kg body weight) GBCA increases sensitivity compared with single-dose (ie, 0·1 mmol/kg body weight) GBCA in detecting enhancing lesions in multiple sclerosis,[20,21] these high doses are not appropriate in clinical practice because of the safety concerns regarding gadolinium deposition. The time delay between contrast administration and T1-weighted acquisition should be identical during follow-up scans and not shorter than 5 min (ideally 10 min). A practical and cost-effective strategy to assure a delay of 5–10 min is the administration of intravenous contrast before the acquisition of T2-weighted and FLAIR sequences (which does not interfere with their visual assessment) and to acquire the postcontrast T1-weighted sequence at the end of the protocol (panels 1, 2).[1,2,22,23] Details on how to obtain contrast-enhanced T1-weighted sequences are included in the appendix (pp 2–3).

Standardised spinal cord MRI protocol for diagnosis

The value of spinal cord MRI for the diagnosis of multiple sclerosis has been unequivocally shown, and it is a key component of the 2017 McDonald criteria. Due to the relatively high proportion of patients with clinically isolated syndrome who show spinal cord lesions (even

Correspondence to:
Prof Àlex Rovira, Section of Neuroradiology, Department of Radiology, Hospital Universitari Vall d'Hebron, Autonomous University of Barcelona, Barcelona 08035, Spain
alex.rovira.idi@gencat.cat

See **Online** for appendix

Panel 1: **Magnetic Resonance Imaging in Multiple Sclerosis–Consortium of Multiple Sclerosis Centres–North American Imaging in Multiple Sclerosis Cooperative recommendations for the use of MRI for establishing multiple sclerosis diagnosis**

Standardised initial brain protocol:
- At least 1·5 T; 3 T if available
- Acquisition and interpretation of 7 T images for clinical routine purposes require dedicated expertise
- Core sequences are: T2-weighted 3D-fluid-attenuated inversion recovery, axial T2-weighted, and T1-weighted with gadolinium (table 2)
- Precontrast T1-weighted sequences are not required

Standardised initial spinal cord protocol:
- 1·5 T or 3 T
- Details on pulse sequences can be found in table 2

Additional or advanced MRI:
- Diffusion-weighted imaging cannot replace gadolinium as a marker for active inflammation
- Dedicated optic nerve MRI is not recommended except for differential diagnosis with neuromyelitis optica spectrum disorders and in patients with atypical clinical features
- There is insufficient current evidence or widespread technology availability to recommend routine use of quantitative MRI techniques and brain volumetric measurements, double inversion recovery or phase-sensitive inversion recovery for cortical lesions, and central vein sign and paramagnetic rims as diagnostic markers

Follow up imaging to establish multiple sclerosis diagnosis when the first MRI does not fulfill the criteria:
- Brain MRI is recommended every 6–12 months in clinically isolated syndrome and subclinical multiple sclerosis radiologically isolated syndrome with risk factors for conversion to multiple sclerosis and paraclinical features of multiple sclerosis
- Spinal cord MRI is not routinely recommended
- Use of gadolinium is not recommended
- Identical image acquisition (ie, standardised repositioning, field strength, pulse sequences, spatial resolution) is strongly recommended

Image interpretation:
- Standardised image interpretation and reporting is recommended
- Knowledge about definition of lesion types is crucial and warning signs against a diagnosis of multiple sclerosis should be recognised
- Standard measures, such as T2 lesion count (ie, if less than 20 T2 lesions in the brain, then provide the exact number, and otherwise report an estimate of between 20 and 50 lesions, between 50 and 100 lesions, more than 100 lesions, or uncountable [ie, confluent] lesions; if <10 lesions in the spinal cord, then provide the exact number, otherwise report more than 10 lesions or diffuse pattern) and gadolinium-enhancing lesion count if gadolinium was administered, are recommended
- Separate identification of cortical lesions (together with juxtacortical lesions) based on standard images (eg, fluid-attenuated inversion recovery; double inversion recovery or phase-sensitive inversion recovery sequences are optional) is recommended

those without spinal cord symptoms), and the lower prevalence of cord lesions in patients with other neurological diseases and in healthy ageing than in patients with multiple sclerosis or clinically isolated syndrome, spinal cord MRI is important not only for showing dissemination in space (DIS) and DIT but also for exclusion of alternative diagnoses (eg, vascular diseases, spinal cord compression, and inflammatory diseases).[6,10,22,24,25] The standardised protocol must include at least two of the following three sagittal sequences: T2-weighted (ie, turbo or fast) spin echo with moderately long echo times, proton density-weighted (ie, turbo or fast) echo, or short tau inversion recovery (STIR). If a GBCA is administered, then a gadolinium-enhanced T1-weighted (ie, turbo or fast) spin echo sequence should be added (table 2). The single acquisition of a T2-weighted sequence is not sufficient, due to its limited sensitivity in depicting signal abnormalities and because a second sequence (ie, proton density-weighted or STIR) is required to confirm the presence of lesions and exclude artifacts.[26,27] Axial images are considered optional. Axial T2-weighted (ie, turbo or fast) spin echo sequences can further improve diagnostic certainty, differentiating multiple sclerosis from mimics (eg, neuromyelitis optica spectrum disorders, MOG-antibody-associated disease) on the basis of lesion extension and topography. Additionally, axial imaging can be useful to confirm and characterise the precise location and extension of lesions that can be seen on sagittal images and to detect small and marginally located lesions that are not seen on the sagittal sequences if there is a high clinical suspicion of spinal cord involvement (table 2, panel 1, figure 2). This protocol is also recommended by the International Conference on Spinal Cord Involvement and Imaging in MS and neuromyelitis optica spectrum disorders.[28]

There are encouraging data for the use of 3D heavily T1-weighted sequences, such as phase-sensitive inversion recovery (PSIR) and magnetisation prepared rapid acquisition of gradient echoes, which have shown a higher sensitivity than STIR and long-echo T2-weighted

images of the cervical spinal cord.[29,30] However, since clinical experience is scarce with these sequences, and because of the lower sensitivity of PSIR in particular compared with STIR sequences in the thoracic segment,[31] PSIR or magnetisation prepared rapid acquisition of gradient echoes sequences cannot be routinely recommended, but could be considered as a fourth alternative to the previously mentioned three standard sequences in centres that have experience using these sequences in clinical practice (table 2). Given that lesions in the lower thoracic spinal segments of the spinal cord can be seen in about 20% (40 of 202) of patients with multiple sclerosis,[32] and involvement of the conus was reported in 33% (5 of 15) of patients with multiple sclerosis myelitis and 41% (21 of 51) of patients with MOG-antibody-associated disease,[33] sagittal MRI scans should ideally cover the whole spinal cord and not just the cervical segment.[22,28,34,35] This strategy entails slightly longer acquisition times compared with scanning only the cervical segment, as an additional sagittal acquisition for the thoracic spinal cord might be needed to obtain images with adequate spatial resolution. However, with the aim of decreasing scanning times without losing substantial sensitivity, and given that few patients with multiple sclerosis have lesions that are exclusively located below the level of the fifth thoracic vertebra (ie, T5),[32] covering only the upper half of the spinal cord (ie, C1 to T5) is a reasonable compromise, unless clinical involvement of the lower cord segment is suspected.

In contrast to brain MRI, there is no evidence that scanning at higher field strengths (ie, 3 T) leads to a higher detection rate of spinal cord lesions than scanning at lower field strengths.[36] Although the occurrence of gadolinium-enhancing lesions in the spinal cord is rare compared with in the brain,[22,25] the use of sagittal gadolinium-enhanced T1-weighted spin echo sequences for diagnostic purposes is recommended. These sequences should be done immediately after the gadolinium-enhanced brain MRI, if both brain and spine scans are done in the same session.

Follow-up imaging to establish MRI-based diagnosis

In patients with a clinically isolated syndrome that is consistent with demyelination in whom the initial brain and spinal cord MRI scans did not show DIS or DIT, according to the 2017 revisions of the McDonald criteria, serial clinical observation and a follow-up MRI are required to identify new disease activity over time. Individuals with multiple sclerosis can have approximately ten new subclinical MRI lesions on T2-weighted MRI for every clinical attack.[37] Serial brain MRI studies in individuals with clinically isolated syndrome showed accrual of new brain T2-weighted lesions that confirmed DIT and diagnosis of multiple sclerosis in 51% of patients by 6 months and in 74% of patients by 12 months.[38]

Although repeating brain MRI to establish DIS and DIT on follow-up MRI scans is recommended, the added value of repeated spinal cord MRI in establishing a multiple sclerosis diagnosis in patients with clinically isolated syndrome is not sufficiently documented,[39] and therefore should be considered on a case-by-case basis. The major drawback of repeated spinal cord imaging is the doubling of the acquisition time with a much lower yield compared with brain imaging. Spinal cord imaging is also technically more demanding (eg, small tissue size and artifacts due to pulsation of vessels and CSF) than is brain imaging. Finally, spinal cord lesions can be subtle, and correct interpretation requires considerable expertise (panel 1).

The interval between the initial and the follow-up brain MRI scans in patients with clinically isolated syndrome should be 6–12 months and clinical assessment should be done during this time interval. This time interval is also applicable for the follow-up of patients with possible subclinical multiple sclerosis (ie, radiologically isolated syndrome) who have the classic paraclinical features of multiple sclerosis and several risk factors on MRI for future confirmation of multiple sclerosis.[40] Showing DIT on a follow-up MRI does not require the detection of gadolinium-enhancing lesions, because DIT can be based exclusively on the detection of new T2 lesions (panels 1, 2).

Additional MRI methods and imaging findings for multiple sclerosis diagnosis

Diffusion-weighted imaging is frequently incorporated into brain imaging protocols for diagnosis and monitoring of multiple sclerosis, but its value is low. Acute demyelinating lesions can present with high signal intensity on diffusion-weighted imaging and a corresponding low apparent diffusion coefficient.[41] This presentation has been proposed as a possible marker to predict blood–brain barrier disruption (ie, gadolinium-enhancement).[41,42] However, insufficient evidence exists to support the use of diffusion-weighted imaging as a marker for acute or

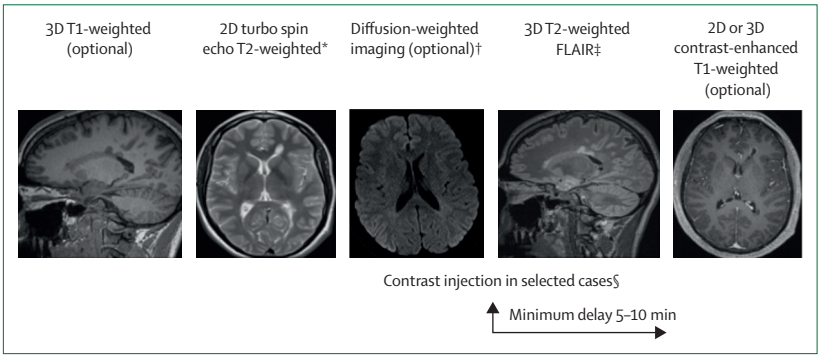

Figure 1: **Recommended brain MRI protocol**
In selected cases, contrast agent can be injected just before the 3D T2-weighted FLAIR; the delay to the start of the 2D or 3D contrast-enhanced T1-weighted imaging should be a minimum of 5–10 min. Spatial resolution parameters for 3D sequences are ≤1 mm × 1 mm × 1 mm (ie, multiplanar reconstruction 3 mm). Spatial resolution parameters for 2D sequences are ≤1 mm × 1 mm × ≤3 mm (table 1). 3D=three dimensional. 2D=two dimensional. FLAIR=fluid-attenuated inversion recovery. *Either single or dual echo. Can be skipped if there is good quality 3D FLAIR in the monitoring protocol. †For differential diagnosis. ‡Transverse 2D FLAIR could be considered as an alternative, if 3D-FLAIR not available or not of good quality. §0·1 mmol/kg bodyweight of macrocyclic agents.

***Panel 2:* Recommendations on the use of gadolinium-based contrast agents in the diagnosis and monitoring of multiple sclerosis**

Diagnosis

The use of gadolinium-based contrast agents is recommended:

- To show dissemination in time on the baseline MRI scan.
- To contribute to differential diagnosis (ie, on the basis of the pattern of enhancement).
- To predict future disease activity and to some extent disease progression.
- For phenotyping patients with progressive disease (ie, active or inactive), if a recent (ie, within 1 year) MRI is not available, and if this information affects treatment decisions.

Monitoring

The use of gadolinium-based contrast agents is recommended:

- In the first year of follow-up (ie, after treatment initiation) if a new baseline MRI scan (ie, usually 3–6 months after treatment initiation) was not obtained, particularly in patients on interferon beta or glatiramer acetate (which are less effective in reducing MRI activity than are other therapies).
- If detection or confirmation of clinical disease activity is required in patients without a recent reference brain MRI scan (done ≤3–6 months ago). MRI should be ideally done as soon as possible and before steroid treatment.
- If showing disease activity with presence of gadolinium-enhancing lesions is required to initiate or change a specific disease-modifying treatment.
- In patients with diffuse and confluent chronic multiple sclerosis lesions (ie, large lesion burden), in which detection of disease activity is required but difficult to show on the basis of new or enlarged T2 lesions.
- For progressive multifocal leukoencephalopathy screening, if there has been a suspicious lesion detected on the standard monitoring or screening brain MRI scan.
- In monitoring of progressive multifocal leukoencephalopathy and detection and monitoring of progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome.

The use of gadolinium-based contrast agents is not recommended:

- To show dissemination in time on serial MRI scans. In case of standard monitoring for subclinical disease activity, if a previous and recent (ie, within approximately 1 year) MRI scan is available that was done with similar technical parameters.
- In new baseline (ie, usually 3–6 months after treatment initiation) MRI scan.
- In short follow-up MRI (ie, within 6 months) done to confirm disease activity in patients with isolated MRI activity on the previous MRI scan.
- For progressive multifocal leukoencephalopathy screening.
- During pregnancy (strictly contraindicated) and lactation (ie, indicated only if essential for patient management).

active inflammation, especially since restricted diffusion is not a specific marker for demyelination. Restricted diffusion is frequently seen in other settings (eg, acute ischaemia and brain abscess) and can aid in lesion differentiation in some cases. However, this sequence should not be used as an alternative to gadolinium-enhanced T1-weighted imaging to show acute demyelinating lesions (panel 1).

Double inversion recovery sequences, particularly in a 3D acquisition, and heavily 3D-T1-weighted sequences, such as PSIR, can improve the detection of cortical multiple sclerosis lesions,[22,23] a feature that was incorporated into the 2017 revisions of the McDonald criteria to show DIS or DIT.[6] As acquisition and interpretation of these sequences, particularly double inversion recovery, can be challenging and are associated with high inter-rater variability,[43] the use of these sequences should be restricted to centres with a sufficient level of expertise with standardisation of image acquisition, to ensure sufficient image quality and expertise with image interpretation, facilitating an accurate lesion assessment (panel 1).

The use of T2*-weighted or susceptibility-weighted sequences, preferably at 3 T in combination with FLAIR sequences to produce so-called FLAIR* images, can show the so-called central vein sign.[44] This sign is emerging as a valuable diagnostic marker for multiple sclerosis, since a high proportion of lesions with the central vein sign suggests multiple sclerosis rather than its mimics.[45–48] Although guidelines regarding image acquisition and interpretation have been published,[49] optimal pulse sequences for detecting this sign (eg, 3D T2*-weighted segmented echo-planar images) are not yet widely available on clinical scanners. Additionally, the proportion of lesions with the central vein sign to be used as a threshold for differentiating multiple sclerosis from other diseases depends on the imaging method. Moreover, the use of a cutoff might be difficult to implement in clinical practice, as it would require all lesions to be counted.[50] Therefore, the central vein sign can be used as a differential diagnostic marker in selected cases and in centres with a standardised, high-level image acquisition and expertise in image interpretation, but its use is not recommended for routine clinical use (panel 1).

Susceptibility-weighted sequences at 3 T can identify paramagnetic rim lesions in around 50% of patients with multiple sclerosis.[51,52] This feature, reflecting iron within phagocytes at the edge of chronic active lesions, rarely occurs in other neurological conditions and therefore has the potential to increase the MRI specificity in differentiating multiple sclerosis from other conditions.[51,52]

However, further studies are required to validate this feature as a diagnostic imaging marker.

Leptomeningeal inflammation in patients with multiple sclerosis has been described in neuropathology studies.[53] Studies using delayed gadolinium-enhanced 3D FLAIR sequences have shown small foci or thin lines of enhancement, suggesting the in-vivo detectability of leptomeningeal inflammation.[54–56] Evidence suggests that leptomeningeal enhancement might be related to subpial demyelination and cortical atrophy.[57–59] However, leptomeningeal enhancement on MRI can also be observed in other chronic neuroinflammatory diseases (eg, neuromyelitis optica spectrum disorders, MOG-antibody-associated disease, and Susac syndrome).[55] Whether this imaging finding reflects ongoing (as opposed to resolved) leptomeningeal inflammation in multiple sclerosis is debated. Therefore, this putative imaging marker of leptomeningeal inflammation is currently not recommended for diagnostic (ie, it cannot be used to show DIS and DIT), prognostic, or monitoring purposes (panel 1).

Optic nerve MRI in patients with optic neuritis can detect T2-hyperintense lesions and even gadolinium-enhancing lesions.[60] MAGNIMS has suggested including optic nerve involvement in the DIS criteria for patients with a first clinical attack.[61] The inclusion of symptomatic optic nerve involvement in DIS for patients with optic neuritis might improve the performance of diagnostic criteria for multiple sclerosis but, as there is no evidence of the added value of including this topography in the context of an initial attack unrelated to the optic nerve, this recommendation was not adopted in the 2017 McDonald criteria. In classic optic neuritis that is suggestive of multiple sclerosis, dedicated optic MRI has no added value in establishing a diagnosis of multiple sclerosis on the basis of the 2017 McDonald criteria[6,62] and is therefore not routinely required. Although optic nerve imaging features in children and adults with neuromyelitis optica spectrum disorders and MOG-antibody-associated demyelination (ie, long lesions, often crossing the chiasm) are often different from optic nerve lesions in patients with multiple sclerosis (ie, typically short segment),[63] the increasing availability and higher specificity of diagnostic antibody testing renders dedicated optic nerve imaging as a diagnostic tool of lesser importance. However, there are some indications for which optic nerve imaging can be useful (panel 3). The standardised optic nerve protocol includes axial and coronal fat-suppressed T2-weighted or STIR and fat-suppressed gadolinium-enhanced T1-weighted sequences (table 1). Studies should be interpreted in conjunction with clinical, neurophysiological (ie, visual evoked potentials), and optical coherence tomography assessment.[60]

Quantitative MRI techniques, including brain volumetric measurements, are increasingly used for research purposes and have been included as secondary outcome measures in several clinical trials. However, evidence is insufficient to support the use of these measures in the routine clinical setting to establish or exclude the diagnosis of multiple sclerosis, particularly because of practical and technical issues (eg, standardisation) in incorporating them into the normal radiological workflow (panel 1).[64,65]

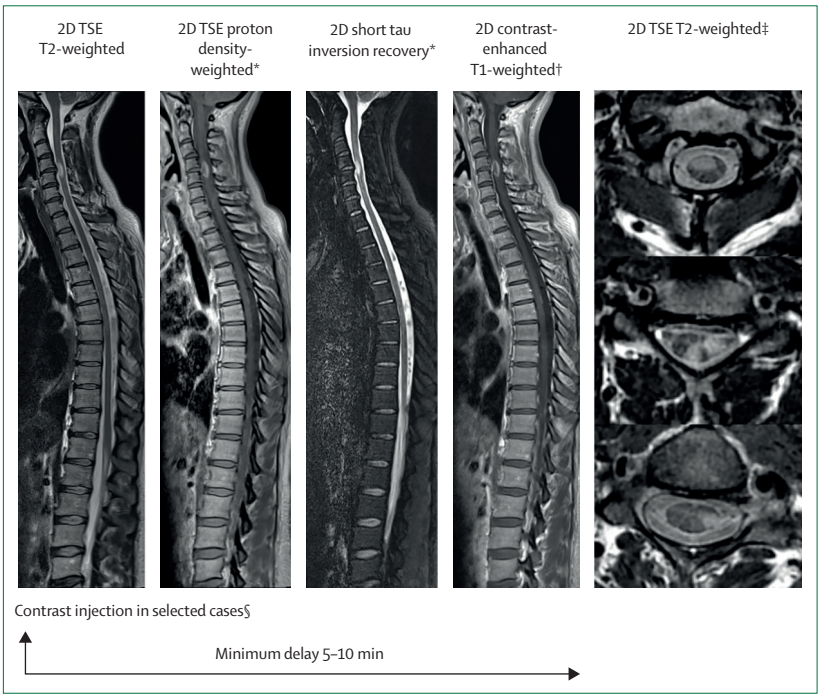

Figure 2: **Recommended spinal cord MRI protocol**
In selected cases, contrast agent can be injected just before the 2D T2-weighted sequence; the time to the end of the 2D contrast-enhanced T1-weighted imaging should be a minimum of 5–10 min. 2D=two dimensional. TSE=turbo spin echo. *Select proton density-weighted sequences or short tau inversion recovery. †Only in selected cases and, if possible, after acquisition of the contrast-enhanced brain MRI (ie, if contrast-enhanced MRI is to be used for both brain and spinal cord, the spinal cord contrast-enhanced T1-weighted sequence should come immediately after the brain contrast-enhanced T1-weighted sequence; minimum delay 5–10 min). ‡Only in selected cases. §0·1 mmol/kg bodyweight of macrocyclic agents.

Monitoring of treatment effectiveness and prediction of treatment response

The increasing number of approved disease-modifying treatments for relapsing multiple sclerosis, and also for primary progressive multiple sclerosis and secondary progressive multiple sclerosis with proven inflammatory disease activity, has further expanded the therapeutic landscape.[66] This expansion further stresses the need for standardised MRI acquisition (ie, reference and follow-up scans) and reporting (appendix pp 4–6) to assess treatment effectiveness and predict treatment response.[67]

Standardised brain and spinal cord MRI protocols

The standardised brain and spinal cord MRI protocols for assessment of disease activity in patients with multiple sclerosis are presented in detail in tables 1, 2. 3D FLAIR sequences outperform 2D sequences in detecting new lesions (ie, improving sensitivity, which is particularly important in the posterior fossa).[13,68] Therefore, when high-quality 3D FLAIR scans (preferably at 3 T) are available, additional T2-weighted sequences are no longer mandatory. An abbreviated

Panel 3: **Indications and objectives for use of spinal cord and optic nerve imaging for diagnosis, prognosis, and monitoring**

Spinal cord

Diagnosis

Clinically isolated syndrome: establishing the diagnosis according to 2017 McDonald criteria[6]

- Detection of symptomatic or asymptomatic spinal cord lesions to show dissemination in space and time

Clinically isolated syndrome: differential diagnosis in case of inconclusive brain MRI findings

- Presence of typical demyelinating spinal cord lesions
- Exclusion of alternative diagnosis (eg, neuromyelitis optica spectrum disorders and MOG-antibody-associated disease)

Primary progressive multiple sclerosis: establishing the diagnosis

- Detection of typical demyelinating spinal cord lesions to show dissemination in space
- Detection of diffuse lesions (ie, diffuse abnormal areas of intermediate signal intensity on proton density-weighted or short tau inversion recovery sequences without a well demarcated border)
- Exclusion of alternative diagnosis (eg, compressive myelopathy)

Prognosis

Radiologically isolated syndrome: prediction of clinically isolated syndrome or multiple sclerosis development

- Detection of asymptomatic spinal cord lesions

Clinically isolated syndrome or early multiple sclerosis: prediction of disability, disability progression, and development of secondary progressive multiple sclerosis

- Detection of spinal cord lesions (ie, active lesions on follow-up MRI scans)

Monitoring

Patients with multiple sclerosis and spinal cord phenotype (ie, no or few brain lesions)

- Detection of active spinal cord lesions

Patients with multiple sclerosis and disability worsening that cannot be explained by brain MRI

- Detection of active spinal cord lesions
- Exclusion of possible comorbidity involving the spine or spinal cord

Patients with multiple sclerosis and repeated spinal cord relapse

- Detection of active spinal cord lesions
- Exclusion of alternative diagnosis or possible comorbidity involving the spinal cord

Treatment switch decision making: inconclusive clinical presentation or brain MRI findings

- Detection of active spinal cord lesions
- Exclusion of possible comorbidity involving the spinal cord

Atypical spinal cord relapse or atypical spinal cord symptoms or signs suggestive of comorbidity

- Detection of active spinal cord lesions
- Exclusion of alternative diagnosis or possible comorbidity involving the spinal cord

Optic nerve

Diagnosis

Clinically isolated syndrome: differential diagnosis

- Atypical isolated optic neuritis; relapsing isolated optic neuritis; chronic relapsing inflammatory optic neuropathy
- Other diseases or factors affecting the optic nerve (eg, neuromyelitis optica spectrum disorders, infectious diseases, vaccination, sarcoidosis, tumours, etc)

Optic neuritis in paediatric patients

- Exclusion of alternative diagnosis (eg, neuromyelitis optica spectrum disorders and MOG-antibody-associated demyelination)

Monitoring

- Patients with multiple sclerosis and new visual symptoms that are suggestive of comorbidity affecting the optic nerve
- Patients with multiple sclerosis and chronic progressive optic nerve symptoms
- Patients with multiple sclerosis and repeated isolated optic nerve relapses

protocol with sagittal 3D FLAIR, including multiplanar reconstructions in axial and sagittal planes and, in selected cases, gadolinium-enhanced T1-weighted sequences, will generally suffice. Additional and alternative pulse sequences for the detection of cortical lesions, such as double inversion recovery and PSIR, can be included but are not recommended as part of the core protocol, in agreement with previous guidelines.[1–3] Also optional are 3D T1-weighted gradient-echo sequences (eg, inversion-recovery or magnetisation-prepared rapid gradient-echo), which are increasingly being acquired for monitoring brain and spinal cord volume change (ie, atrophy). Although evidence is insufficient to recommend routine use of quantitative MRI sequences, optic nerve imaging, non-conventional MRI sequences, or volumetric measures,[60,64] these approaches, if acquired with a standardised protocol, can provide additional information in selected cases.

MRI measures for the assessment of disease activity

In the 2015 MAGNIMS and 2016 CMSC guidelines, the use of GBCAs for the assessment of disease activity, particularly for effectiveness monitoring purposes, was recommended.[2,3] Given the evidence regarding gadolinium-deposition in the brain, which is much higher in patients receiving linear compared with macrocyclic

Panel 4: **Magnetic Resonance Imaging in Multiple Sclerosis–Consortium of Multiple Sclerosis Centres–North American Imaging in Multiple Sclerosis Cooperative recommendations for the use of MRI for monitoring treatment effectiveness and assessment of disease activity**

MRI timing

Obtain a baseline brain MRI (with gadolinium if required by drug label) before starting or switching disease-modifying treatment.

Obtain a new baseline brain MRI usually at 3–6 months after treatment onset to avoid misinterpretation of lesions that developed before therapeutic onset. Longer intervals are to be considered in patients who are treated with disease-modifying therapies that are slow acting.

Obtain a new baseline MRI usually at 3–6 months after treatment initiation without gadolinium unless highly active disease at baseline or unexpected clinical activity.

Consider gadolinium-enhanced MRI on first follow-up scan after treatment initiation in the absence of a new baseline scan.

Obtain yearly brain MRI while the patient is on the disease-modifying treatment; consider longer intervals in clinically stable patients after the first few years of treatment, particularly if safety monitoring is not required.

In patients who show MRI disease activity that is not associated with clinical activity on a follow-up scan, consider a new MRI scan without gadolinium 6 months later.

MRI acquisition

Identical slice positioning, pulse sequences, magnetic field strengths, and spatial resolution are highly recommended. Brain MRI should be done according to the standardised acquisition protocol (tables 1, 2).

- Abbreviated MRI protocol (ie, 3D T2-weighted fluid-attenuated inversion recovery; optional gadolinium-enhanced T1-weighted sequences) can be sufficient.
- Use of gadolinium-based contrast agents is optional and not recommended for all clinical situations (ie, consider new or enlarging T2 lesions as the only measure when a recent [ie, ≤1 year] reference scan is available); use gadolinium judiciously; minimise repeated gadolinium imaging when possible and use a single dose (table 2, panel 2).

Spinal cord MRI is not routinely recommended to detect subclinical activity; in clinical situations requiring spinal cord MRI (panel 3), images should be acquired according to a high-quality standardised protocol (tables 1, 2).

Optic nerve MRI is not routinely recommended to detect subclinical activity. In clinical situations requiring optic nerve MRI (panel 3), images should be acquired according to a high-quality standardised protocol (tables 1, 2).

MRI reporting in the clinical setting

Report active (new or enlarging) T2 lesions.

Co-registration, fusion, and subtraction techniques are helpful, especially if T2 lesion load is high.

Recognise poor sensitivity of routine MRI for cortical grey matter lesions.

Focal leptomeningeal gadolinium-enhancement cannot yet be considered a reliable marker for active inflammatory disease activity.

Volumetric and quantitative MRI measures, including commercially approved automated segmentation techniques, are not routinely recommended.

chelates,[7] the European Medicines Agency suspended the use of linear GBCAs for CNS MRI examinations and recommended that gadolinium should be used only if essential, and at the lowest possible dose.[8] The US Food and Drug Administration stated that health-care professionals should consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary and urged them to assess the necessity of repetitive GBCA MRI scans in established treatment protocols (panel 2).[69]

The policy of reducing GBCA use in patients with multiple sclerosis in the pharmacovigilance setting is reasonable. New or enlarging (ie, active) T2 lesions are a reliable marker of active inflammatory disease and can be superior to gadolinium-enhancing lesions in many clinical situations, such as routine follow-up in the short term to detect subclinical disease activity, if a technically comparable previous and recent (ie, done within ≤1 year) MRI scan is available. The use of GBCAs should, generally, be limited to patients for whom detection or confirmation of recent (ie, within 1 year) clinical disease activity is required for treatment decisions and patient management (eg, initiating or escalating therapy), certainly when a recent previous and technically comparable MRI scan is not available, or when assessment of disease activity based on active T2 lesions can be difficult (ie, patients with high or chronic lesion burden; panel 2).[70] The value of GBCAs and the importance of new T2 lesions applies to patients with progressive multiple sclerosis, who present with gadolinium-enhancing lesions less frequently than do patients with relapsing multiple sclerosis (panels 2, 4).[71,72]

Novel MRI measures of chronic active lesions include slowly expanding lesions, defined as concentric regions of existing lesions showing local expansion and often progressive hypointensity on T1-weighted scans. These lesions reflect ongoing tissue loss and their presence has been proposed as an MRI marker of chronic inflammatory activity.[73,74] Slowly expanding lesions are more frequent in patients with progressive multiple sclerosis but also occur in patients with relapsing multiple sclerosis.[75] Given the slow progression of these lesions, the absence of pathological data supporting their association with

inflammation, and the highly standardised (and often multiple) follow-up scans that are needed to correctly identify them, their use is technically challenging and therefore cannot be recommended for routine clinical use. Studies suggest that multiple sclerosis lesions with a paramagnetic rim on magnetic susceptibility-based sequences are accompanied by ongoing chronic inflammatory demyelination, tend to expand slowly over time, and are associated with more aggressive disease.[76,77] However, their identification is not yet standardised and thus cannot be routinely recommended.

Diffuse abnormal white and grey matter of the brain and spinal cord, defined as areas of mild T2 signal increase without well demarcated borders, can reflect diffuse and widespread inflammation, demyelination, and neurodegeneration, and are more prominent in patients with primary progressive and secondary progressive multiple sclerosis.[78] In clinical practice, it is difficult to reliably quantify the severity and extent of these changes. Therefore, such findings are also not recommended for diagnostic and monitoring purposes.

Automated registration, fusion, and subtraction tools are becoming available in clinical image-interpretation software packages. Although they are not yet widely used because clinicians are unfamiliar with their use, these tools can further enhance sensitivity for detection of active T2 lesions, particularly in patients with a high load of T2 lesions.[79,80] In particular, subtraction tools are widely available and are already being used for different purposes in clinical practice (appendix p 7). Some automated segmentation-based tools that are commercially available for new lesion detection have received Conformité Européenne or US Food and Drug Administration approval, or both. Major points of criticism of these tools include the scarcity of clinical validation studies and the requirement for strict standardisation of image acquisition (ie, identical MRI system, pulse sequences, and acquisition parameters). Therefore, insufficient evidence exists to recommend their routine clinical use (panel 4).

The emerging role of leptomeningeal inflammation in patients with multiple sclerosis was discussed earlier. Foci of leptomeningeal gadolinium enhancement are more frequent in patients with secondary progressive multiple sclerosis than in patients with other types of multiple sclerosis.[75,81] However, once apparent, the foci are generally constant over a long period of time, and no effect of disease-modifying treatments has been shown on the size or number of foci.[54] Therefore, this imaging marker is not recommended to monitor progression of multiple sclerosis (panel 4).

New cortical grey matter lesions during the disease course contribute to disease progression, particularly in certain groups of patients: those with relapsing-remitting multiple sclerosis and long disease duration; and those with progressive disease, who have an increased grey matter lesion load compared with patients presenting with clinically isolated syndrome or early relapsing-remitting multiple sclerosis.[82] The use of cortical lesions as a marker of individual disease progression in clinical practice is possible but requires a high degree of expertise in image analysis and standardisation of image acquisition (panel 4).

The prevalence and relevance of asymptomatic spinal cord lesions in patients with relapsing multiple sclerosis might have been understated in previous MRI guidelines, leading to a recommendation not to use spinal cord MRI for assessing disease activity or treatment effectiveness in clinical routine. Studies indicate that asymptomatic spinal cord lesions might not be accompanied by new asymptomatic brain lesions in approximately 10% (10 of 103) of clinically stable patients with relapsing-remitting multiple sclerosis (ie, without new relapses during the interval between scans),[39] indicating that a relevant proportion of patients with active disease would be missed if spinal cord MRI scans were not routinely done in addition to brain MRI scans.

Repeated spinal cord imaging can be useful in patients with multiple sclerosis with clinical disease progression that cannot be explained by brain MRI findings or for pending decisions about switching treatments. The importance of spinal cord lesions is even more evident in patients with progressive multiple sclerosis because spinal cord lesions are related to disability progression, and regular spinal cord MRI (eg, every 2–3 years) can aid in treatment decisions in these patients.[83] The challenges of high-quality image acquisition and interpretation that could lead to inaccurate lesion detection, subsequent inappropriate clinical treatment decisions (eg, treatment escalation), and the associated increase in the total scanning time and costs, need to be weighed against the possible gain of sensitivity of spinal cord MRI for assessing disease activity. Therefore, although spinal cord MRI for monitoring purposes would be desirable, especially when treatment decisions have to be made for patients who have progressive multiple sclerosis and a spinal cord MRI that was done many years earlier, this examination is not recommended routinely with the exception of specific clinical situations (panels 3, 4).

Prediction of treatment response

Prediction of individual treatment response is a major challenge in patients with multiple sclerosis, particularly in view of the increasing number of disease-modifying treatments with different effectiveness and adverse event profiles. Thus, early detection of patients who are at high risk of a suboptimal response is important to allow a prompt treatment switch or escalation.

Extensive literature examines various prognostic scores for identifying treated patients with high risk of developing relapses and disability worsening; these studies were discussed in detail in the previous guidelines[2] and are further supported by other studies.[84,85] Models for the prediction of treatment response are mainly based on clinical and MRI measures that are collected one year

after treatment onset, although one study showed the possibility to refine and personalise the prediction of treatment effect by use of pre-treatment demographic, clinical, and radiological characteristics.[86] The presence of active lesions on brain MRI, either at baseline or during the first year after treatment onset, has been identified as a powerful predictive measure, underlining that an accurate assessment of MRI disease activity is essential. To achieve this accurate assessment, a new baseline brain MRI scan obtained 3–6 months after treatment onset is generally recommended (panel 4). This strategy respects the therapeutic lag time of disease-modifying treatments and avoids the decision that a treatment is not effective on the basis of MRI activity within the first weeks or months after treatment initiation. A new baseline brain scan that is done more than a few months after treatment initiation is recommended for patients who are treated with disease-modifying treatments that require a long period of time to reach their full effect[86,87] (eg, glatiramer acetate, which takes up to 9 months to become effective) or with induction therapies, for which there is no value of obtaining a new baseline MRI scan until completion of the full initial course (figure 3).[88,89] Gadolinium-enhanced T1-weighted sequences are recommended for detecting disease activity on MRI scans that are done before the start of some disease-modifying treatments, if showing acute inflammatory activity is required by the label. Gadolinium-enhanced MRI is not required for the new baseline MRI, as disease activity on this scan can be based on detection of new T2 lesions, except in patients with highly active disease at baseline or in patients with unexpected clinical activity after treatment initiation, in whom gadolinium-enhanced MRI can be useful to identify lesion activity. In the absence of a new baseline scan, gadolinium-enhanced T1-weighted sequences done 3–6 months after treatment onset can also be helpful to identify ongoing activity because interval active T2 lesions might be related not to ineffective treatment but to the therapeutic lag of the drug during the first few months of therapy (panel 4).[90]

In patients who show asymptomatic disease activity on a follow-up MRI scan, an additional scan 6 months later, generally without gadolinium, can be considered if continued disease activity could have an effect on management. Similarly, in patients with suspected clinical activity that is not confirmed on brain or spinal cord MRI, a new brain MRI scan 6 months later can be considered. In these situations, the persistence of clinical or radiological disease is sufficient to identify patients with suboptimal treatment response.[91] MRI activity on this new follow-up scan can be defined exclusively by new or enlarging T2 lesions, without the need for gadolinium-enhanced scans (panel 4).

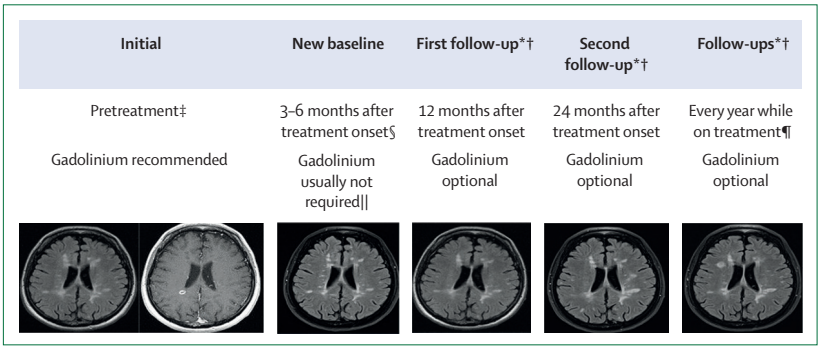

Figure 3: **MRI timing in monitoring of multiple sclerosis**
Images show scans from a single patient over time. *Shorter follow-up MRI (ie, 6 months) if substantial isolated MRI activity or isolated clinical activity. †Add spinal cord MRI to brain MRI if clinically indicated (panel 3). ‡Add spinal cord MRI to brain MRI if never done. §Longer intervals to be considered in patients treated with disease-modifying treatments (eg, up to 9 months with glatiramer acetate and until completion of the full initial course with induction therapies). ¶Less frequent MRI in clinically stable patients treated with interferon beta or glatiramer acetate. ||Consider gadolinium administration in patients with highly active disease at baseline or in patients with unexpected clinical activity after treatment initiation.

MRI for monitoring drug safety

The important role of brain MRI in safety monitoring has been stressed by the increasing number of approved disease-modifying treatments that prevent inflammatory disease activity via suppressing or modulating the immune system. The spectrum of possible safety events is broad and not exclusively restricted to opportunistic infections.[92] Non-infectious CNS comorbidities, such as vascular or neoplastic processes, and atypical demyelinating lesions that potentially mimic multiple sclerosis (which can be related to treatment) might require dedicated imaging protocols, including contrast-enhanced T1-weighted sequences.[93–95]

Progressive multifocal leukoencephalopathy (PML) is particularly relevant due to the relatively high incidence of this opportunistic infection in patients who are treated with natalizumab. However, PML is not exclusively related to natalizumab and has been associated, albeit with much lower frequency, with other multiple sclerosis therapies.[96–99] The imaging findings of patients with early PML and the clinical relevance of brain MRI screening to facilitate early PML diagnosis, leading to a more favourable outcome, have been shown in patients with multiple sclerosis who are treated with natalizumab.[100] The abbreviated brain MRI protocol that is recommended for PML screening is given in table 2 and includes FLAIR, T2-weighted, and diffusion-weighted imaging sequences (appendix p 7). If high-quality 3D FLAIR sequences are available, then conventional T2-weighted sequences are optional. Gadolinium-enhanced T1-weighted images are recommended if a new suspicious lesion is detected on surveillance MRI[2] and in the follow-up of PML lesions for early detection and monitoring of inflammatory PML and PML-immune reconstitution inflammatory syndrome (panels 2, 5).[101–103]

Several risk stratification and screening schemes for PML in patients who are treated with natalizumab are currently used in clinical practice; these schemes are based on anti-JC virus antibody index values, treatment duration, and previous use of immunosuppressive

Panel 5: **Magnetic Resonance Imaging in Multiple Sclerosis–Consortium of Multiple Sclerosis Centres–North American Imaging in Multiple Sclerosis recommendations for the use of MRI for monitoring treatment safety**

General

- Consider opportunistic infections, other medication-related safety events (eg, posterior reversible encephalopathy, acute ischaemic stroke, and haemorrhagic stroke), and even comorbidities that might not be directly related to the specific multiple sclerosis treatment.

Progressive multifocal leukoencephalopathy (PML) screening and detection

- Obtain annual brain MRI according to the standardised acquisition protocol (table 1).
- Do frequent PML screening (ie, every 3–4 months) with an abbreviated MRI protocol (ie, fluid-attenuated inversion recovery, T2-weighted, and diffusion-weighted imaging) exclusively for patients who are treated with natalizumab and have a high risk of PML occurrence (ie, patients who are seropositive for JC virus and have been treated with natalizumab for ≥18 months, with high anti-JC virus antibody index values [>0·9], or previously treated with immunosuppressive therapies). If high-quality 3D fluid-attenuated inversion recovery scans are available, conventional T2-weighted sequences are optional.
- Use gadolinium-based contrast agents to further assess lesions that are suggestive of PML on screening MRI (panel 2).
- Use gadolinium-based contrast agents to detect and monitor PML-immune reconstitution inflammatory syndrome (panel 2).
- Spinal cord MRI is not required for treatment safety monitoring.
- Consider continuous lesion enlargement and typical PML-immune reconstitution inflammatory syndrome on MRI as supportive of PML, even when JC virus DNA is not detected in the CSF.

Potential for carry-over PML

- Do clinical and radiological (ie, brain MRI) baseline evaluation before switching from disease-modifying treatment that is associated with an increased risk of PML.
- Do MRI based pharmacovigilance by use of frequent brain MRI, according to the abbreviated MRI acquisition protocol (table 1), every 3–4 months up to 9–12 months after natalizumab treatment switch in patients at high risk for PML.

therapies.[103–105] One study provides evidence that an MRI screening interval of 3–4 months is associated with lower PML lesion volume at diagnosis and a better outcome than is routine yearly monitoring,[106] and this protocol is recommended for patients with multiple sclerosis who are treated with natalizumab and have a high risk of PML occurrence (ie, patients who are seropositive for JC virus and have been treated with natalizumab for ≥18 months, with a high anti-JC virus antibody index [>0·9] or previous history of immunosuppressive treatment). This approach is also recommended in patients who are treated with natalizumab with extended dosing intervals and are at high risk of PML, although the anticipated risk of PML might be lower compared with patients receiving the normal interval dosing scheme.[107] Special caution is required in patients who are being switched to other therapies, as development of PML or other opportunistic infections can still occur (ie, so-called carry-over cases). A new baseline brain MRI scan and enhanced pharmacovigilance with frequent MRI monitoring every 3–4 months, up to 9–12 months after initiation of the new treatment, is justified (panel 5).

Importantly, small PML lesions, such as those that are observed in asymptomatic PML, might be associated with an absence of detectable JC virus DNA in the CSF.[108] Although detectable JC virus DNA in the CSF is required for the diagnosis of definite and probable PML, its absence is not conclusive.[108,109] Enlargement of the suspected PML lesion and typical PML-immune reconstitution inflammatory syndrome on follow-up MRI should be considered as supportive of a PML diagnosis regardless of negative CSF results, even when repeated tests have been done (panel 5).[101,110,111]

Diagnosis and monitoring of paediatric patients with multiple sclerosis

The 2017 McDonald criteria can accurately diagnose paediatric multiple sclerosis (ie, patients diagnosed with multiple sclerosis before age 18 years), even in children younger than 11 years. When applied at the time of a first attack (provided that criteria for acute disseminated encephalomyelitis are not met),[112] these criteria show similar sensitivity and specificity for relapsing-remitting multiple sclerosis as in adult-onset cohorts. Exclusion of other diagnoses, including MOG-antibody-associated disease and AQP4-positive neuromyelitis optica spectrum disorder, is advised. Over 50% of children with an incident demyelinating attack have a monophasic illness with no evidence for relapsing-remitting multiple sclerosis at 5 years after their first attack.[113,114] Few of these children meet 2017 McDonald criteria at onset (and none of them meet the criteria over time, given absence of clinical or MRI activity) and many have transient anti-MOG antibodies. MRI features of MOG-related demyelination often include hazy, ill-defined, large T2 lesions; prominent lesions involving the cerebellar peduncles; long bilateral optic nerve lesions with almost routine inclusion of the intraorbital segments; and long spinal cord lesions, often including the conus.[63,115]

Panel 6: **Magnetic Resonance Imaging in Multiple Sclerosis–Consortium of Multiple Sclerosis Centres–North American Imaging in Multiple Sclerosis recommendations for the use of MRI in patients with multiple sclerosis in childhood or during pregnancy and lactation**

MRI in paediatric patients with multiple sclerosis

MRI acquisition:

- Use the same standardised brain and spinal cord MRI protocols as for adults (tables 1, 2); gadolinium-enhanced images are valuable to exclude non-multiple sclerosis diagnosis at onset but are optional for monitoring purposes (panel 2).
- Full spinal cord MRI should be obtained for diagnosis of children with spinal cord symptoms or signs or with inconclusive brain MRI findings; in other cases, spinal cord MRI could be obtained to provide a baseline MRI; spinal cord MRI is not recommended for regular monitoring, but can be considered if clinically warranted (table 2).
- Dedicated optic nerve MRI is not recommended, except for differential diagnosis with MOG-antibody-associated demyelination or anti-AQP4 antibody disease and if clinical features are atypical (table 1).

Frequency of MRI scanning and assessing imaging measures:

- Use similar scan frequency for monitoring the disease and therapeutic effectiveness as for adults. Increase frequency of imaging (eg, every 6 months) in children with highly active disease or in situations where imaging evidence of treatment benefit aids in advocacy for access to therapies that are approved only for adults with multiple sclerosis.
- Use similar scan frequency for safety monitoring (eg, progressive multifocal leukoencephalopathy screening) as for adults.

MRI measures:

- For detecting MRI activity, reliance on new or enlarging T2 lesions is better than gadolinium-enhancing lesions.
- Brain or spinal cord atrophy and quantitative MRI methods are not recommended for diagnostic and routine clinical monitoring purposes.

MRI during pregnancy

- MRI is not strictly contraindicated during pregnancy; however, the need for MRI during pregnancy should be assessed on a case-by-case basis (eg, clinical presentation that is suggestive of unexpected disease activity or comorbidity, such as cerebral venous thrombosis).
- Use standardised protocols (tables 1, 2) and a magnetic field strength of 1·5 T.
- Gadolinium-based contrast agents during pregnancy are contraindicated (panel 2).
- New or enlarged T2 lesions can be used for detection of disease activity.

MRI during post partum and lactation

- There is no limitation to use of MRI in the post-partum phase.
- MRI acquisition should be done according to standardised protocols (tables 1, 2).
- The administration of gadolinium-based contrast agents during lactation should be allowed only if highly necessary for diagnostic or monitoring purposes but, if macrocyclic gadolinium-based contrast agents are given, then it might be possible to continue breastfeeding (panel 2).
- Active T2 (ie, new or enlarged) lesions are the preferred measure for inflammatory disease activity.
- A new baseline brain MRI after pregnancy (ie, 2–3 months post partum) is recommended.

In addition to brain MRI, spinal cord MRI is recommended as part of the diagnostic evaluation of a child with possible multiple sclerosis. Spinal cord MRI is important, especially in cases of children with spinal cord symptoms or signs or with inconclusive brain MRI findings (panel 6). In other cases, including patients with non-spinal cord symptoms or signs, it might be useful to have a baseline spinal cord MRI, but the length of the protocol and the need for sedation should be considered, together with the knowledge that spinal cord MRI yields only a 10% increase in confirmation of multiple sclerosis diagnosis at onset (because most paediatric patients meet the criteria on the basis of having a high number of cerebral lesions).[116]

Primary progressive multiple sclerosis is not a paediatric condition, and thus any child with slowly progressive neurological deficits should undergo a comprehensive metabolic, genetic, rheumatological, oncological, and infectious disease evaluation.[117] Of note, some mitochondrial diseases and some forms of leukodystrophy are associated with clinical features (ie, pseudorelapses and improvement with corticosteroids) and imaging features (ie, gadolinium enhancement and expanding T2 lesions) that are consistent with inflammation.[118]

In children with multiple sclerosis, MRI is useful for documentation of new disease activity, for adjudication of treatment effectiveness, and as an outcome measure in clinical trials, similar to its usefulness in adults. Lesions can show a greater tendency to improve or resolve in children with multiple sclerosis compared with adults.[115] However, compared with multiple sclerosis in adults, paediatric multiple sclerosis is associated with a higher early relapse rate; children accrue an average of nine new T2 lesions within the 6 months after their first attack.[119] Brain MRI scans every 6 months are advised in children with highly active disease and as evidence to evaluate therapeutic effectiveness (panel 6).

Parents are understandably apprehensive about the use of gadolinium, and children often wish to avoid intravenous line insertion, further emphasising the goal to reduce the use of GBCAs to the initial diagnostic

examination and follow-up studies where a specific concern is raised. Paediatric-onset multiple sclerosis is associated with less brain growth than expected for their age followed by brain atrophy,[120] although measures of brain volume are currently obtained only in research or clinical trial contexts.[121]

Monitoring of patients with multiple sclerosis during pregnancy and lactation

Multiple sclerosis disease activity can fluctuate during pregnancy and post partum, particularly during lactation. Additionally, comorbidities that are related or unrelated to the pregnancy can mimic multiple sclerosis disease activity and affect clinical decision making. Pregnancy (particularly during the first trimester) has been considered as a contraindication for MRI, because of the potential risk to the fetus,[122,123] even though evidence suggests no increased risk of stillbirth, neonatal death, congenital anomalies, neoplasm, or hearing loss.[124] Therefore, MRI can be done if deemed necessary, on a case-by-case basis, considering that some sequences and target organs (eg, brain *vs* spinal cord) lead to different energy deposition to the fetus.[122,123] Although 1·5 T and 3 T MRI examinations produce equivalent energy deposition in most cases, some sequences at 3 T produce higher energy deposition to the fetus[125] and, as hyperthermia to the fetus has been associated with neural tube and facial defects,[126,127] field strengths greater than 1·5 T are not recommended in pregnant women (panel 6).

GBCAs can cross the placenta: gadolinium is excreted into the amniotic fluid and dissociated free gadolinium can potentially be recirculated to the fetus.[128] Data for the use of GBCAs in pregnant women are scarce, although one study suggests an association with stillbirth, neonatal death, and rheumatological, inflammatory, and dermatological diseases.[123] Additionally, the effect on long term outcomes in children has not been fully investigated. Therefore, the use of GBCA is contraindicated during pregnancy (panels 2, 6).

MRI during the post-partum period might be clinically indicated in the case of suspected disease activity or to acquire a new baseline T2-lesion load and determine accrual of new lesions compared with before pregnancy. Post-partum multiple sclerosis disease activity can reach the pre-pregnancy level or even rebound above that.[129] Although MRI assessment just before pregnancy is desirable, in practice it can be difficult to achieve (panel 6).

With respect to GBCAs, a small proportion of the gadolinium administered (ie, less than 0·04%) passes into breast milk. Consequently, it is estimated that a fetus is exposed to less than 1% of the permitted gadolinium dose for neonates[130] and the use of GBCAs is not strictly contraindicated during lactation.[131] Although many clinicians recommend that breastfeeding mothers dispose of their breast milk for at least 24 h after undergoing a gadolinium-enhanced MRI, the latest European Society of Urogenital Radiology guidelines state that breastfeeding can be continued normally when macrocyclic GBCAs are administered (panels 2, 6).[131]

Conclusions

The 2021 evidence-based MAGNIMS–CMSC–NAIMS international consensus recommendations on the use of MRI in multiple sclerosis diagnosis, prognosis, and disease monitoring unify recommendations from European and North American expert groups and address major issues concerning the use of MRI in clinical practice that have arisen in the past few years. Adherence to the proposed standardised brain and spinal cord MRI protocols provides an important step towards a better harmonisation of indications, image acquisition, and interpretation. In these new recommendations, we further simplified and shortened the brain MRI protocol for monitoring purposes, thereby making it easier and more likely to be used than previous guidelines.[1–3] We also recommend a new baseline brain MRI scan without gadolinium at least 3 months after treatment initiation and annual follow-up scans after that without gadolinium.

A novel recommendation compared with the previous guidelines[1–3] is to reduce the repeated use of even macrocyclic GBCAs despite the absence of convincing evidence for clinical consequences. As GBCAs are not necessary in many clinical situations, particularly during monitoring of treatments for multiple sclerosis, their judicious and scarce use seems prudent.

We conclude that there is not enough evidence to recommend spinal cord MRI for routine follow-up monitoring of disease activity in patients with multiple sclerosis, as it is technically challenging and would disproportionately increase the scanning time. However, obtaining spinal cord MRI is important for diagnosis, when assessing the initial extent of CNS involvement (ie, disease burden), and in other special circumstances, including unexplained and unexpected disease worsening and the possibility of a diagnosis other than multiple sclerosis. We have clarified that the recommendations for MRI in the diagnosis, prognosis, and monitoring of patients with multiple sclerosis are

Search strategy and selection criteria

References for this Position Paper were identified by reviewing our personal files and through searches of National Center of Biotechnology Information PubMed for manuscripts that were published in English between Jan 1, 1990, and Feb 6, 2021, with the terms "multiple sclerosis", "guidelines", "treatment/therapy", "Standardized examination", "disease monitoring" "magnetic resonance imaging OR MRI", "pharmacovigilance", and "paediatric MS" and assorted combinations of the following terms: "pharmacovigilance", "adverse event", "infection", "progressive multifocal leukoencephalopathy OR PML", "Multiple sclerosis OR MS", "treatment monitoring", "safety monitoring", "magnetic resonance imaging OR MRI", "paediatric", "pregnancy", and "post partum". We reviewed reference lists of relevant articles and review articles for additional references. The final reference list was generated on the basis of originality, recency, and relevance to the scope of this Position Paper.

equally applicable in most situations to both paediatric and adult-onset disease.

Finally, although we appreciate the accumulating evidence, we cannot yet recommend implementation of volumetric analysis, newly described imaging features, and quantitative MRI measures in routine clinical practice. The most promising of these techniques are high-resolution susceptibility-based MRI, for detecting the central vein sign and discriminating chronic active lesions, and new approaches to identifying cortical lesions. However, further validation studies in clinical practice are urgently required.

The value of quantitative changes in brain and spinal cord volume measures as predictors of the evolution of multiple sclerosis and in monitoring the effects of treatment has been shown in research settings and clinical trials. However, to make implementation of volume measurements in routine clinical practice feasible, several potential sources of error—including, but not limited to, confounding physiological factors on brain volume measures and the accuracy, reproducibility, and value of volumetric tools—need to be appropriately accounted for and managed. Standardisation and implementation of new and potentially more sensitive and specific imaging techniques than those that are currently used represent two of the greatest challenges but also two of the greatest opportunities in the near future, particularly as new treatments focusing on neuroprotection, remyelination, and neuronal repair emerge.

Contributors

MPW and ÀR designed the programme agenda for the MAGNIMS workshop that served as the basis of this Position Paper, prepared the initial drafts of this manuscript, edited the manuscript, and approved the final version for submission. FF contributed to the content of the manuscript. All other authors contributed to the content of the Position Paper and edited the final manuscript.

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