International 2020 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in multiple sclerosis

Abstract:

The 2015 MAGNIMS and 2016 CMSC guidelines on the use of magnetic resonance imaging (MRI) in diagnosis and monitoring of multiple sclerosis (MS) have 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 MS patient management and care. These 2020 revision of the guidelines on MRI in MS merge recommendations from MAGNIMS, CMSC, and NAIMS, and translate recent research findings to clinical practice to improve the use of MRI for diagnosis, prognosis and monitoring of individuals with MS. We recommend changes in the MRI acquisition protocols such as emphasising the value of 3D-FLAIR as the core brain pulse-sequence to improve diagnostic accuracy and better enable identification of new lesions to monitor treatment efficacy and we provide recommendations for the judicious use of gadolinium-based contrast agents for specific clinical purposes. In addition, we focus of certain aspects of progressive MS and extend the recommendations to the use of MRI in paediatric MS, during pregnancy, and in the postpartum period. Finally, we discuss promising MRI approaches that may deserve introduction in clinical practice in the near future.

Key words:

Multiple sclerosis; MR imaging; Standardized examination; Diagnosis; Demyelination; Guidelines; Neurodegeneration; Disease monitoring; Atrophy; Progressive multifocal leukoencephalopathy; Safety monitoring

Introduction

The value of magnetic resonance imaging (MRI) in multiple sclerosis (MS) for diagnostic, prognostic, and monitoring purposes is well established and its implementation has been specified in several consensus and guidelines papers that slightly vary across the world. Yet universal adoption of a standardized approach to MRI in clinical practice, including image acquisition protocols and timing of scans, remains a major challenge because of differences in health care systems and clinical practices between countries. The 2015 MAGNIMS (Magnetic Resonance Imaging in MS)[1,2] and 2016 CMSC (Consortium of Multiple Sclerosis Centers)[3] consensus guidelines on the use of MRI in MS diagnosis, prognosis, and monitoring guided (neuro)radiologists and neurologists to standardize the 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 (Gd)-based contrast agents (GBCAs) due to the potential risk of Gd accumulation in the brain,[7,8] and emerging evidence regarding the role of spinal cord MRI for prognosis and monitoring of MS patients. These and other new developments in the use of MRI in MS prompted a critical review of the recent literature and a revision of the 2015 MAGNIMS consensus guidelines, as well as harmonization of the recommendations with new revisions of the 2016 CMSC guidelines and viewpoints of the North-American Imaging in MS cooperative (NAIMS).

These 2020 MAGNIMS-CMSC-NAIMS international consensus recommendations on MRI in MS provide updated recommendations on how and when to use MRI in MS diagnosis, prognosis, and treatment monitoring with special focus on the use of standardized MRI protocols, the judicious use of GBCAs, and standardized reporting. In addition, we extend the recommendations to the use of MRI in special populations and situations such as progressive and paediatric MS, during pregnancy, and in the postpartum 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 MS convened in Graz, Austria, on 12 and 13 April 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 separately and independently in Newark, New Jersey, USA, on 25 October, 2019 including members of the CMSC and the North American Imaging in MS (NAIMS) cooperative. Following discussion amongst the chairs of the MAGNIMS, NAIMS, and CMSC Working Groups, representatives of the NAIMS and CMSC group 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 supplementary material.

MS diagnosis

The 2017 revisions of the McDonald criteria on MS diagnosis reinforced the importance of brain and spinal cord MRI examinations, in addition to the clinical presentation (in the context of a clinical event suggestive of a first attack of MS) and cerebrospinal fluid analysis (i.e., demonstration of oligoclonal bands) under certain circumstances.[6,9] The 2017 revisions of the McDonald criteria also highlighted the strong need for strict standardization of MRI acquisition and interpretation to avoid misdiagnosis.[6,10,11] The crucial need for a standardized brain and spinal cord MRI acquisition and reporting (supplementary material) at the time of the first clinical presentation and during the early course of MS goes beyond diagnostic purposes since it provides important prognostic information (supplementary material).[12,13]

Standardized brain MRI protocol for MS diagnosis

Previous MAGNIMS and CMSC guidelines recommended the use of axial single (late echo) or dual echo T2-weighted (T2w) (turbo/fast) spin echo (SE) sequences, axial and sagittal T2w fluid attenuated inversion recovery (FLAIR), and contrast enhanced axial T1-weighted (T1w) sequences, preferably at 3 Tesla (T).[1,3] The 2017 revisions of the McDonald diagnostic criteria themselves do not require substantial changes to this standardized protocol. However, 3 dimensional (D) acquisition techniques (particularly for FLAIR and T1w sequences) are now preferred, as these have become more routinely available on clinical scanners and improve both lesion detection and the realignment of anatomic orientation necessary to detect new lesions, when comparing serial MR studies (Tables 1 and 2, Figure 1).[14] Based on its high sensitivity, the 3D FLAIR acquisition is considered the "core sequence" for MS diagnosis and monitoring (see sections

below on efficacy and safety monitoring). However, in centres that are unable to acquire 3D FLAIR images with sufficient image quality, high quality 2D pulse-sequences (≤3mm slice thickness and no gap) can provide an acceptable alternative. Pre-contrast T1-weighted sequences do not have added value for routine clinical purposes and are not required.

Even though 3T scanners provide a higher MS lesion detection rate and offer the potential of shorter acquisition times compared to lower-field magnets, there is no evidence to support that 3T MRI actually leads to an earlier diagnosis of MS.[15,16] The use of 1.5T scanners continues to be sufficient for brain lesion detection at the time of diagnosis, as long as scans are of good quality with adequate signal-to-noise and spatial resolution (≤ 1mm x 1mm pixel in-plane resolution). The use of scanners with field strengths <1.5T is not recommended (Table 1).

Ultra-high-field MRI operating at 7T has been used for research purposes and has added value with respect to the detection of cortical grey matter lesions.[17-19] However, 7T systems are not widely available and are mostly used for research purposes. In addition, 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 is therefore not recommended at this stage.

The administration of GBCAs has been discussed following the recognition of Gd-deposition in the central nervous system (CNS), leading to specific use recommendations by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).[7,8] However, the use of GBCAs continues to be invaluable during the initial work-up of MS in order to demonstrate dissemination in time (DIT) and to exclude alternative diagnoses.[6,10] Despite prior findings that double- and triple-dose (0.2 and 0.3 mmol/kg body weight) GBCA increases sensitivity compared to single-dose (0.1 mmol/kg body weight) in detecting enhancing lesions in MS,[20,21] it is not appropriate to use these high doses in clinical practice because of the safety concerns regarding Gd-deposition. The time delay between contrast administration and T1w acquisition should be identical during follow-up scans and not shorter than 5 minutes (ideally 10 minutes). A practical and cost-effective strategy to assure a delay of 5–10 min is to perform the contrast injection before the acquisition of T2w and FLAIR sequences (which does not interfere with their visual assessment), and acquire the post-contrast T1w sequence at the end of the protocol (details on how to obtain contrast-enhanced T1w sequences are included in the supplementary material).[1,2,22,23]

Standardized spinal cord MRI protocol for MS diagnosis

The value of spinal cord MRI for the diagnosis of MS has been unequivocally demonstrated, and it is a key component of the 2017 McDonald criteria. Due to the relatively high proportion of patients with CIS - even without spinal cord symptoms - who show spinal cord lesions, and the lower prevalence of cord lesions in other neurologic diseases and in healthy aging, spinal cord MRI is important not only for demonstration of dissemination in space (DIS) and DIT, but also for exclusion of alternative diagnoses (e.g., vascular diseases, cord compression, and inflammatory diseases).[6,10,22,24,25] The standardized protocol must include at least two of the following three sagittal sequences: (i) T2w (turbo/fast) SE with moderately long echo times; (ii) proton-density (PD) (turbo/fast) SE; (iii) short-tau inversion recovery (STIR). If contrast is administered, a Gd-enhanced T1w (turbo/fast) SE sequence should be added (Table 3). The single acquisition of a T2w sequence is not sufficient, due to its limited sensitivity in depicting signal abnormalities and a second sequence (PD or STIR) is required to confirm the presence of lesions and exclude artefacts.[26,27] Axial T2w (turbo/fast) SE sequences can further improve diagnostic certainty differentiating MS from mimics (e.g., Neuromyelitis Optica Spectrum Disorders [NMOSD], Myelin Oligodendrocyte Glycoprotein [MOG] antibody-associated disease) and are can be useful to confirm and characterize lesions seen on sagittal images or to detect lesions in spinal cord segments with high clinical suspicion of involvement (Table 3, Figure 2). This protocol is also recommended by the International Conference on Spinal Cord Involvement and Imaging in MS and NMOSD.[28] There is encouraging data on the use of 3D heavily T1w sequences, such as phase-sensitive inversion recovery (PSIR) and magnetization prepared rapid acquisition of gradient echoes (MPRAGE), which have shown a higher sensitivity compared to STIR and long-echo T2w images in the cervical spinal cord.[29,30] However, since clinical experience is limited with these sequences, and because of the lower sensitivity of PSIR in particular compared to STIR sequences in the thoracic segment,[31] PSIR or MPRAGE sequences cannot be routinely recommended, but could be considered as a fourth alternative to the above three standard sequences in centres with relevant experience (Table 3). Given the presence of lesions in the lower segments of the spinal cord (including the conus medullaris) are common, sagittal MRI scans should ideally cover the whole spinal cord and not just the cervical segment.[22,28,32,33] This strategy entails slightly longer acquisition times, as an additional sagittal acquisition for the thoracic cord may be needed in order to obtain images with adequate spatial resolution. However, with the aim of decreasing scanning times without losing significant sensitivity, and given

that the minority of MS patients have lesions exclusively located below the level of the 5th thoracic vertebra (T5),[34] covering only the upper half of the spinal cord (C1 to T5) is a reasonable compromise for monitoring purposes, 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 (i.e., 3T) leads to a higher detection rate of spinal cord lesions.[35] Although the occurrence of Gd-enhancing lesions in the spinal cord is relatively rare compared to the brain,[22,25] the use of sagittal Gd-enhanced T1w SE sequences for diagnostic purposes is recommended, and they should be performed immediately after the Gd-enhanced brain MRI, if both brain and spine scans are performed in the same session.

Follow-up imaging to establish MRI-based diagnosis

In patients with a Clinically Isolated Syndrome (CIS) consistent with demyelination in whom the initial brain and spinal cord MRI scans did not demonstrate DIS and/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. In individuals with MS, new T2 lesions in the brain outnumber clinical attacks by a ratio of approximately 10 subclinical MRI lesions for every clinical attack.[36] Serial brain MRI studies in individuals with CIS show accrual of new brain T2 lesions that confirm DIT and MS diagnosis in 51% by 6 months and in 74% by 12 months.[37]

Whilst 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 an MS diagnosis in CIS is not sufficiently documented,[38] and therefore should be considered on a case-by-case basis (Table 4). The major drawback of repeated spinal cord imaging is the doubling of the acquisition time with a much lower yield compared to brain imaging. Spinal cord imaging is also technically more demanding. Finally, spinal cord lesions can be subtle, and correct interpretation requires considerable expertise.

The interval between the initial brain and the follow-up MRI scans in CIS patients should be 6–12 months and should be combined with clinical assessment. This time interval is also applicable for the follow-up of patients with possible subclinical MS (i.e., Radiologically Isolated Syndrome [RIS]) with the classical paraclinical features of MS and several MRI risk factors for future confirmation of MS.[39] The demonstration of DIT on a follow-up MRI does not require the detection of Gd-enhancing lesion(s), as it can be based exclusively on the detection of new T2 lesion(s) (Table 5).

Additional MRI methods and imaging findings for MS diagnosis

Diffusion-weighted imaging (DWI) is frequently incorporated into brain imaging protocols for MS diagnosis and monitoring, but its value is limited. Acute demyelinating lesions can present with high signal intensity on DWI and corresponding low apparent diffusion coefficient (ADC).[40] This has been proposed as a possible marker to predict blood-brain-barrier disruption (i.e., Gd-enhancement).[40,41] However, there is insufficient data supporting the use of DWI as a marker for acute/active inflammation, especially since restricted diffusion is not a specific marker for demyelination, but is frequently seen in other settings (e.g., acute ischemia, brain abscess). Hence, this sequence should not be used as an alternative to Gd-enhanced T1w imaging.

Double Inversion Recovery (DIR) sequences, particularly in a 3D acquisition, as well as **heavily 3D T1-weighted sequences** such as PSIR, can improve the detection of cortical MS lesions,[22,23] a feature now incorporated into the 2017 revisions of the McDonald criteria for the demonstration of DIS or DIT.[6] As acquisition and interpretation of these sequences, particularly DIR, can be challenging and is associated with high inter-rater variability,[42] the use of these sequences should be restricted to centres with a sufficient level of expertise.

The use of **T2*/susceptibility-weighted (SWI)** sequences, preferably at 3T in combination with FLAIR sequences to produce so-called FLAIR* images, may show the "central vein sign."[43] The central vein sign is emerging as a valuable diagnostic marker for MS, since a high proportion of lesions with this sign suggests MS rather than its mimics.[44-47] Guidelines regarding image acquisition and interpretation have been published.[48] However, optimal pulse sequences (e.g., T2*w segmented echo-planar images) are not yet widely available on clinical scanners. In addition, the proportion of lesions with the central vein sign to be used as a threshold for differentiating MS from other diseases depends on the imaging method and potentially other factors. Moreover, the use of a cut-off may be difficult to implement in clinical practice, as it requires that all lesions are counted.[49] Therefore, the central vein sign may be used as a (differential) diagnostic marker in selected cases, and in centres with a standardized and high-level image acquisition and with expertise in image interpretation, but it is not recommended for routine clinical use.

SWI at 3T can identify paramagnetic rim lesions in around 50% of MS patients. 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 MR specificity in differentiating MS from non-MS.[50,51] However, further studies are required to validate this feature as a diagnostic imaging marker.

Leptomeningeal inflammation in MS has been described in neuropathology studies.[52] Recently, studies using delayed Gd-enhanced 3D FLAIR have demonstrated small foci or thin lines of enhancement suggesting the in vivo detectability of leptomeningeal inflammation.[53-55] It has been suggested that leptomeningeal enhancement might be related to subpial demyelination and cortical atrophy development.[56-58] However, leptomeningeal enhancement on MRI can also be observed in other chronic neuroinflammatory diseases (e.g., NMOSD, MOG antibody-associated disease, Susac syndrome).[54] Whether this imaging finding reflects ongoing (as opposed to resolved) leptomeningeal inflammation in MS remains under debate. Therefore, this putative imaging marker of leptomeningeal inflammation is currently not recommended for diagnostic, (i.e., it cannot be used to demonstrate DIS and DIT), prognostic, or monitoring purposes.

Optic nerve MRI in patients with optic neuritis can detect T2-hyperintense lesions and even Gd-enhancing lesions in the optic nerve.[59] MAGNIMS have suggested including optic nerve involvement in the DIS criteria in patients with a first clinical attack.[60] The inclusion of symptomatic optic nerve involvement in DIS in patients with optic neuritis may improve the performance of diagnostic criteria for MS, but as no additional value was found in the context of an initial attack unrelated to the optic nerve, this recommendation was not adopted in the 2017 McDonald criteria. In classical optic neuritis suggestive of MS, dedicated optic MRI has no added value in establishing a diagnosis of MS based on the 2017 McDonald criteria[6,61] and is therefore not routinely required. While optic nerve imaging features in children and adults with NMOSD and MOG antibody associated demyelination (long lesions, often crossing the chiasm) are often different from optic nerve lesions in MS (typically short segment),[62] the increasing availability and higher specificity of diagnostic antibody testing renders dedicated optic nerve imaging as a diagnostic tool of lesser importance even in these patients. However, there are some indications in which optic nerve imaging may be useful (Table 6). The standardized optic nerve protocol includes axial and coronal fat-suppressed T2w or STIR (Short Tau Inversion Recovery) and fat-suppressed Gd-enhanced T1w sequences (Table 1). Studies should be interpreted in conjunction with clinical, neurophysiological, and optical coherence tomography (OCT) assessment.[59]

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, there is still not enough evidence to support the use of these measures in the routine clinical setting

to establish or exclude the diagnosis of MS, particularly because of practical and technical issues (e.g., standardization) in incorporating them into the normal radiologic workflow.[63,64]

Box 1: MAGNIMS/CMSC/NAIMS recommendations for the use of MRI for establishing MS diagnosis	
Standardized brain protocol:	• At least 1.5T; 3T if available • Acquisition and interpretation of 7T images for clinical routine purposes require dedicated expertise • Core sequences are: T2-weighted 3D-FLAIR, axial T2-weighted, and T1-weighted with Gd (Table 2). Pre-contrast T1-weighted sequences not required
Standardized spinal cord protocol:	• 1.5 or 3T • See Table 3 for details on pulse sequences
Additional/advanced MRI:	• DWI cannot replace Gd as a marker for active inflammation • Dedicated optic nerve MRI is not recommended except for differential diagnosis with NMOSD and in cases 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 - DIR and/or PSIR for cortical lesions - Central vein sign and paramagnetic rims as diagnostic markers
Follow-up imaging to establish MS diagnosis:	• Brain MRI is recommended every 6–12 months in CIS and subclinical MS (i.e., "high-risk" RIS: with risk factors for conversion to MS and paraclinical features of MS) • Spinal cord MRI is not routinely recommended • Use of Gd is not recommended • Identical image acquisition (i.e., standardized repositioning, field strength, pulse sequences, spatial resolution) is strongly recommended
Image interpretation:	• Standardized image interpretation and reporting is recommended • Knowledge about definition of lesion types is crucial and red-flags should be recognized • Standard measures (T2 lesion count*, Gd lesion count if Gd was administered) are recommended • Separate identification of cortical lesions (together with juxtacortical lesions) based on standard images, e.g. FLAIR (DIR/PSIR sequences optional)

***** Suggested system for reporting total T2 lesion number: Brain: If <20 lesions, provide exact number; otherwise, report an estimate of "between 20 and 50 lesions," "between 50 and 100 lesions," "more than 100 lesions," or "uncountable (confluent) lesions." Spinal cord: If <10 lesions, provide exact number; otherwise, report "more than 10 lesions" or "diffuse pattern."

Monitoring of treatment efficacy and prediction of treatment response

The increasing number of approved disease-modifying treatment (DMTs) for relapsing MS, and more recently for primary progressive MS (PPMS) and secondary progressive MS (SPMS), has further expanded the therapeutic landscape.[65] This further stresses the need for standardized MRI acquisition (reference and follow-up scans) and reporting (supplementary material) to assess treatment efficacy and predict treatment response.[66]

Standardized brain and spinal cord MRI protocols

The standardized brain and spinal cord MRI protocols for assessment of disease activity in MS patients are presented in detail in Tables 1, 2, and 3. 3D FLAIR sequences outperform 2D sequences in detecting (new) lesions (improving sensitivity, which is particularly important in the posterior fossa).[13,67] Therefore, when high-quality 3D FLAIR scans (preferably at 3T) are available, additional T2w sequences are no longer mandatory. An abbreviated protocol with 3D FLAIR, including multiplanar reconstructions in axial and sagittal planes and, in selected cases, Gd-enhanced T1w sequences, generally suffice. Additional and alternative pulse sequences for the detection of cortical lesions, such as DIR and PSIR, can be included but do not belong to the core protocol. Also optional are 3D T1w gradient-echo sequences (e.g., inversion-recovery- or magnetization-prepared gradient echo), which are increasingly being acquired for monitoring brain volume change (atrophy). Although there is insufficient evidence to recommend routine use of quantitative MR sequences, optic nerve imaging, non-conventional MR sequences, and volumetric measures,[68,69] these approaches, if acquired with a standardized protocol, may 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, in particular for efficacy monitoring purposes, was recommended.[2,3] Given the evidence regarding the Gd-deposition in the brain which is much higher in patients receiving linear compared to macrocyclic chelates,[70] the EMA suspended the use of linear GBCAs for CNS MRI examinations, and recommended that Gd should only be used if essential, and at the lowest possible dose.[71] The FDA 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 are also urged to assess the necessity of repetitive GBCA MRIs in established treatment protocols.[72]

In MS, the policy of reducing GBCA use in MS patients in the pharmacovigilance setting is reasonable. New and/or enlarging (active) T2 lesions are a reliable marker of active inflammatory disease and may be superior to Gd-enhancing lesions in many clinical situations such as routine short-term follow-up to detect subclinical disease activity, if a technically comparable previous and relatively recent (≤1 year) MRI scan is available. The use of GBCAs should, in general, be limited to cases where detection or confirmation of recent clinical disease activity is required for treatment decisions and patient management (e.g., initiating or escalating therapy), certainly when a recent previous and technically comparable MRI is not available, or when assessment of disease activity based on active T2 lesions can be difficult (patients with high (chronic) lesion burden) (Table 5).[73] The limited value of GBCA and the importance of new T2 lesions certainly applies to progressive MS patients presenting less frequently with Gd-enhancing lesions.[74,75]

Novel MRI measures of chronic-active lesions include the so-called **"slowly expanding lesions"** (SELs), defined as concentric regions of existing lesions showing local expansion and oftentimes progressive hypointensity on T1w scans. These lesions reflect ongoing tissue loss and their presence has been proposed as an MRI marker of chronic inflammatory activity.[76,77] SELs are more frequent in progressive MS patients but also occur in relapsing MS.[78] Given the slow progression of these lesions, lack of pathological data confirming their association with inflammation, and the highly standardized (often multiple) follow-up scans needed to correctly identify them, their use is technically challenging, and therefore cannot be recommended for routine clinical use. Recent data suggest that MS lesions with a hypointense 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.[79,80] However, their identification is not yet standardized and thus cannot be routinely recommended.

Diffuse abnormalities in the white and grey matter of the brain and spinal cord can reflect diffuse and widespread inflammation, demyelination, and neurodegeneration, and are more prominent in SP and PP MS.[81] In clinical practice, it is difficult to reliably quantify the severity/extent of these changes. Therefore, such findings are also not recommended for diagnostic and monitoring purposes.

Automated registration/fusion/subtraction tools are becoming available in clinical image interpretation software packages and can further enhance sensitivity for detection of active T2 lesions (Figure 3), particularly in patients with high T2 lesion load.[82,83] Some commercially available automated tools for new lesion detection have received Conformité Européenne (CE) and/or FDA approval. Major points of criticism include lack of clinical validation data and the requirement for strict standardization of image acquisition

(i.e., identical MR system, pulse sequences, acquisition parameters). Therefore, there is insufficient evidence to recommend their routine clinical use.

The emerging role of **leptomeningeal inflammation** in MS is discussed in the MS diagnosis section. Foci of leptomeningeal Gd-enhancement are more common in SPMS patients.[78,84] However, once apparent, they generally remain constant over a long period of time, and no effect of DMTs on this finding has been demonstrated.[53] Therefore, this imaging marker is not recommended for MS disease monitoring purposes.

New **cortical grey matter lesions** during the disease course reflect individual disease progression, particularly in late relapsing and progressive MS patients who typically show an increased grey matter lesion load.[85] 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 standardization of image acquisition.

The prevalence and relevance of **asymptomatic spinal cord lesions** in relapsing MS patients may have been understated in previous MRI guidelines, leading to a recommendation not to use spinal cord MRI for assessing disease activity/treatment efficacy in clinical routine. Recent data indicate that asymptomatic spinal cord lesions may not be accompanied by new asymptomatic brain lesions in approximately 10% of clinically stable relapsing MS patients,[86] indicating that a relevant proportion of active patients would be missed if spinal cord MRI scans were not routinely performed in addition to brain MRI scans. The importance of spinal cord lesions is even more evident in progressive MS patients.[87] The challenges of high quality image acquisition and interpretation that could lead to inaccurate lesion detection, and consequent inappropriate clinical treatment decisions (e.g., 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, spinal cord MRI is not generally recommended but can be useful in specific clinical situations (see Table 4).

Box 3: MAGNIMS/CMSC/NAIMS recommendations for the use of MRI for MS treatment efficacy monitoring and disease activity assessment

MR acquisition:

- Identical slice positioning, pulse sequences, magnetic field strengths, and spatial resolution
- Brain MRI according to the standardized acquisition protocol (Table 1)
    - Abbreviated MRI protocol (3D T2-weighted FLAIR; optional Gd-enhanced T1-weighted) can be sufficient
    - Use of GBCAs is optional and not recommended for all clinical situations (consider new and/or enlarging T2 lesions as only measure when a recent reference scan is available); use Gd judiciously; minimize repeated Gd imaging when possible and use a single dose (Table 3)
        - Spinal cord MRI not recommended to detect subclinical activity; in clinical situations requiring spinal cord MRI (Table 4), acquire images according to a high-quality standardized protocol (Table 2)
        - Optic nerve MRI not recommended to detect subclinical activity (Table 1)

MR reporting in the clinical setting:

- Report active (new/enlarging) T2 lesions
- Co-registration/fusion/subtraction techniques are helpful, especially if T2 lesion load is high
- Recognize poor sensitivity of routine MRI for cortical grey matter lesions
- Focal leptomeningeal Gd-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

Prediction of treatment response

Prediction of individual treatment response is a major challenge in MS, particularly in view of the increasing number of DMTs with different efficacy and adverse event profiles. Thus, early detection of patients at high risk of a suboptimal response is important to allow a prompt treatment switch or escalation.

There is extensive literature examining a variety of prognostic scores for identifying treated patients with high risk of developing relapses and disability worsening; these were discussed in detail in the previous guidelines and are further supported by recent data.[2,88,89] Current models for the prediction of treatment response are mainly based on clinical and MRI measures collected one year after treatment onset, although a recent study demonstrated the possibility to refine and personalize the treatment effect by using pre-treatment demographic, clinical, and radiological characteristics.[90] The presence of active lesions on brain MRI, either at baseline or during the first years after treatment onset, has been identified as a very powerful predictive measure, underlining that an accurate assessment of MRI disease activity remains

essential. To achieve this, a re-baseline brain MRI scan obtained 3–6 months after treatment onset is generally recommended. This strategy respects the therapeutic lag time of DMT and avoids the inappropriate attribution to treatment failure judged by MRI activity detected within the first weeks/months after treatment initiation before drugs become effective. A re-baseline brain scan performed at longer intervals is recommended in patients treated with DMTs that require longer periods to reach their full effect,[90,91] e.g., certain injectables (up to 9 months with glatiramer acetate), and with induction therapies in which there is no value of obtaining a re-baseline MRI until completion of the full initial courses (Figure 4).[92,93] Gd-enhanced T1w sequences are recommended for detecting disease activity on MRI scans performed prior to start of certain DMTs, if the demonstration of recent inflammatory activity is required by the label. Gd-enhanced MRI is not required for the re-baseline MRI, as disease activity 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 Gd-enhanced MRI may be useful to identify current lesion activity. In the absence of a re-baseline scan 3-6 month after treatment onset, Gd-enhanced T1w sequences can also be helpful to identify ongoing activity, as interval active T2 lesions may not be related to treatment failure but to the drug's therapeutic lag during the first few months of therapy.[94]

In patients with demonstrate asymptomatic disease activity on a follow-up MRI, an additional scan 6 months later, generally without Gd, can be considered if continued disease activity could have an impact on patient management. Similarly, in patients with suspected clinical activity, not confirmed on brain or spinal cord MRI, a new brain MRI obtained 6 months later can be considered. In these situations, the persistence of clinical or radiological disease might better identify patients with suboptimal treatment response.[95] MRI activity on this new follow-up scan can be based exclusively by virtue of new or enlarging T2 lesions, without the need for Gd-enhanced scans.

Box 4: MAGNIMS/CMSC/NAIMS recommendations for the use of MRI for predicting treatment response
• Obtain baseline brain MRI (with Gd if required by label) prior to starting or switching DMT • Obtain re-baseline brain MRI usually at 3–6 months after treatment onset to avoid misinterpretation of lesions that developed prior to therapeutic onset of the DMT. Longer intervals are to be considered in patients treated with slow-acting DMTs • Obtain re-baseline MRI without Gd unless highly active disease at baseline or unexpected clinical activity after treatment initiation • Consider Gd-enhanced MRI on first post-treatment follow-up in the absence of a re-baseline scan • Obtain yearly brain MRI while on DMT; consider longer intervals in clinically stable patients after the first few years, particularly if safety monitoring is not required • In patients who demonstrated MRI disease activity not associated with clinical activity on a follow-up scan, consider a new MRI without Gd 6 months later

MRI for drug safety monitoring

The important role of brain MRI in safety monitoring has been stressed by the increasing number of approved DMTs that have a more robust impact on preventing MS 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.[96] Non-infectious CNS comorbidities, such as vascular or neoplastic processes, might also be unrelated to treatment.[97-99]

Progressive multifocal leukoencephalopathy (PML) is of particular relevance due to the relatively high incidence of this opportunistic infection in patients treated with natalizumab. However, PML is not exclusively related to natalizumab and has been associated, albeit with much lower frequency, wiht other MS therapies.[100-103] The imaging findings of (early) PML and the clinical relevance of brain MRI screening to facilitate early PML diagnosis leading to a more favourable outcome have been demonstrated in natalizumab-treated MS patients.[104] The recommended abbreviated brain MRI protocol recommended for PML screening is given in Table 2 and includes FLAIR, T2w, and DWI sequences (Figure 5). Gd-enhanced T1w images are only recommended if a new (suspicious) lesion is detected on surveillance MRI.[2,61] If high-quality 3D FLAIR sequences are available, conventional T2w sequences are optional.

Several risk stratification and PML screening schemes in natalizumab-treated patients, based on the JC virus antibody index values, treatment duration and immunosuppressive therapies in the past, are currently used in clinical practice.[105,106] Recent data provides evidence that an MRI screening interval of 3–4 months is associated with lower PML lesion volume at diagnosis and a better outcome,[107] and this is rec-

ommended for natalizumab-treated MS patients with higher risk of PML occurrence (i.e., JC virus seropositive patients treated with natalizumab for ≥18 months with high JC antibody index (>0.9), or history of prior immunosuppressive treatment). This approach is also recommended in high risk natalizumab-treated patients with extended dosing intervals, although the anticipated risk of PML might be lower compared to patients receiving the normal interval dosing scheme.[108] Special caution is required in patients being switched to a lower-risk MS therapy, as development of PML or other opportunistic infections can still occur ("carry-over" cases). A re-baseline brain MRI and enhanced pharmacovigilance with frequent MRI monitoring every 3–4 months, up to 9–12 months after initiation of the new treatment, is justified.

Importantly, smaller PML lesions, such as those observed in asymptomatic PML, might be associated with absence of detectable JC virus DNA in the CSF.[109] Although demonstration of CSF JC virus DNA is required for the diagnosis of definite and probable PML, its absence is not conclusive.[109,110] Enlargement of the suspected PML lesion and typical PML-IRIS (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 performed.[111-113]

Box 5: MAGNIMS/CMSC/NAIMS recommendations for the use of MRI for MS treatment safety monitoring

General

- Consider opportunistic infections, other medication-related safety events (e.g., posterior reversible encephalopathy, acute ischemic and haemorrhagic strokes), and even comorbidities that might not be directly related to the specific MS treatment

Progressive multifocal leukoencephalopathy (PML) screening and detection

- Obtain annual brain MRI according to the standardized acquisition protocol (Table 1)
- Perform frequent PML screening (every 3–4 months) using an abbreviated MR protocol (FLAIR, T2-weighted, DWI) exclusively for natalizumab-treated MS patients with high risk of PML occurrence. * If high-quality 3D FLAIR scans are available, conventional T2-weighted sequences are optional.
- Use GBCA to further assess lesions suggestive of PML on screening MRI
- Spinal cord MRI is not required for treatment safety monitoring
- Consider continuous lesion enlargement and typical PML-IRIS on MRI as supportive of PML, even when JC virus DNA is not detected in the CSF

Potential for carry-over PML

- Perform clinical and radiological (brain MRI) baseline evaluation before switching from DMT associated with a risk of PML
- Perform MRI based pharmacovigilance using 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

* High risk: JC virus seropositive patients treated with natalizumab for ≥18 months, with high JC virus antibody index values (>0.9), or previously treated with immunosuppressive therapies.[105,106]

Paediatric MS

The 2017 McDonald criteria accurately diagnose paediatric MS, even in children less than 11 years, and when applied at the time of a first attack (provided that criteria for acute disseminated encephalomyelitis are not met),[114] they show with similar sensitivity and specificity as in adult-onset MS. Exclusion of other diagnoses including anti MOG and AQP4-positive NMOSD is advised. Over 50% of children with an incident demyelinating attack have a monophasic illness with no evidence for relapsing MS at 5 years,[115,116] few of these children meet 2017 McDonald criteria at onset (and none over time, given absence of clinical or MRI activity), and many have transient MOG antibodies. MRI features of MOG-related demyelination often include hazy ill-defined large T2 lesions, prominent lesions involving the cerebellar peduncles, long-length bilateral optic nerve lesions with almost routine inclusion of the intra-orbital segments, and long spinal cord lesions often including the conus.[117]

Spinal cord MRI should be performed in all children with spinal cord symptoms, and in those with non-spinal cord symptoms where spinal lesions aid in MS diagnosis. While spinal cord lesions contribute to the DIS criteria, spinal cord MRI yields only a 10% increase in confirmation of MS diagnosis at onset given that criteria are met by the high number of cerebral lesions in most paediatric MS patients.[118] The routine addition of spinal cord MRI at the time of diagnostic conclusive brain MRI in young children with non-spinal cord symptoms might be useful as a baseline spinal cord MRI exam, but must be balanced against the need of prolonged sedation.

PPMS is not a paediatric condition, and thus any child with slowly progressive neurological deficits should undergo a comprehensive metabolic, genetic, rheumatologic, oncologic, and infectious disease evaluation.[119] Of note, some mitochondrial diseases and some forms of leukodystrophy are associated with clinical (pseudo-relapses, improvement with corticosteroids) and imaging features consistent with inflammation (e.g., Gd-enhancement, expanding T2 lesions).[120]

Serial MRI documentation of new disease activity, adjudication of treatment efficacy, and as an outcome measure in clinical trials aligns with its utility in the adult MS context. In contrast to adults, paediatric MS is associated with higher early relapse rate than adult MS; children accrue an average of 9 new T2 lesions within the six months after their first attack.[121] Brain MRI scans every 6 months is advised in children with highly active disease and as evidence to support access to highly efficacious therapies currently approved for adult MS.

Parents are understandably apprehensive about the use of Gd, and children often wish to avoid intravenous line insertion, further emphasizing the goal to limit the use of GBCAs to the initial diagnostic examination and follow-up studies where a specific concern is raised.

Paediatric-onset MS associates with failure of age-expected brain growth followed by brain atrophy in adolescence,[122] although such measures are currently only obtained in research or clinical trial contexts.[123] Brain volumes must be normalized to age and sex-expected measures. Brain volume curves in boys and girls are distinctly different, and intracerebral structures (normalized for brain size) also differ by sex.

Box 7: MAGNIMS/CMSC/NAIMS recommendations for the use of MRI in paediatric MS

MR acquisition:

- Use the same standardized brain and spinal cord MRI protocols as for adults (Tables 1 and 2).
    - Gd-enhanced images are valuable to exclude non-MS diagnosis at onset but are optional for monitoring purposes (Table 3)
- Full spinal cord MRI must be obtained for diagnosis of children with spinal cord symptoms or with inconclusive brain MRI findings; in the remaining cases spinal cord MRI could be obtained in order to have a baseline MRI; spinal cord MRI is not recommended for regular monitoring but can be considered if clinically warranted (Table 4)
- Dedicated optic nerve MRI is not recommended except for differential diagnosis with MOG-related demyelination or NMOSD, 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 efficacy as for adults MS. Perform more frequent imaging (e.g., every 6 months) in children with highly active disease or in situations where imaging evidence of treatment benefit aids in advocacy for special access to therapies only approved for adult MS
- Use similar scan frequency for safety monitoring (e.g., PML screening) as for adults

MRI measures

- New or enlarging T2 lesions are favoured over Gd enhancing lesions
- Brain/spinal cord atrophy and quantitative MRI methods are not recommended for diagnostic and routine clinical monitoring purposes

MS monitoring during pregnancy and lactation

MS disease activity can fluctuate during pregnancy and postpartum, particularly during lactation. In addition, comorbidities related or unrelated to the pregnancy can occur, mimicking MS disease activity and affecting clinical decision-making. Pregnancy (particularly during the first trimester) has been considered as a relative contraindication for MRI, because of the potential risk to the foetus,[124,125] even though recent

evidence suggests no increased risk of stillbirth, neonatal death, congenital anomalies, neoplasm, or hearing loss[126] Therefore, MRI can be performed if deemed necessary, on a case-by-case basis.[124,125] Although 1.5T and 3T MRI examinations produces equivalent energy deposition in most cases, some sequences at 3T produce higher energy deposition to the foetus,[127] and as hyperthermia to the foetus has been associated with neural tube and facial defects,[128,129] it is not recommended to use field strengths >1.5T in pregnant women.

GBCAs can cross the placenta, Gd is excreted into the amniotic fluid, and dissociated free Gd can potentially be recirculated to the foetus.[130] Data on the use of GBCAs in pregnant women are rather limited, although recent data suggest an association with stillbirth and neonatal death as well as rheumatological, inflammatory, and dermatological diseases.[125] In addition, the effect on longer term outcomes in children has not been fully investigated. Therefore, the use of GBCA is contraindicated during pregnancy.

MRI during the postpartum period might be clinically indicated in the case of suspected disease activity or in order to acquire a new baseline T2 lesion load and determine accrual of new lesions compared to pre-pregnancy. Postpartum MS disease activity can reach the pre-pregnancy level or even rebound above that.[131] Although MRI assessment just before pregnancy is desirable, in practice it may be difficult to achieve.

With respect to GBCAs, a proportion of the Gd administered passes into breast milk, but the use of GBCAs is not strictly contraindicated during lactation.[132] Although many clinicians recommend that breastfeeding mothers “pump and dump” their breast milk for at least 24 hours after undergoing a Gd-enhanced MRI, the latest European Society of Urogenital Radiology (ESUR) guidelines are that breastfeeding may be continued normally when macrocyclic GBCAs are administered.[133]

Box 8: MAGNIMS/CMSC/NAIMS recommendations for the use of MRI during pregnancy and lactation

Pregnancy:

- MRI is not strictly contraindicated during pregnancy; however, the need for an MRI during pregnancy should be limited and assessed on a case-by-case basis (e.g., clinical presentation suggestive of unexpected disease activity or comorbidity, such as cerebral venous thrombosis)
- Use standardized protocols (Tables 1 and 2) a magnetic field strength of 1.5T
- GBCAs during pregnancy is contraindicated (Table 3)
- New or enlarged T2 lesions for detection of disease activity

Post-partum and lactation:

- There is no limitation to use MRI in the post-partum phase
- MRI acquisition should be performed according to standardized protocols (Tables 1 and 2)
- The administration of GBCAs during lactation should be restricted, but if macrocyclic GBCAs are given, it may be possible to continue breastfeeding
- Active T2 (new/enlarged) lesions is the preferred measure for inflammatory disease activity.
- A re-baseline brain MRI after pregnancy (2–3 months post-partum) is recommended

Conclusions

The 2020 evidence-based MAGNIMS-CMSC-NAIMS international consensus recommendations on the use of MRI in MS 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 standardized brain and spinal cord MRI protocol provides an important step towards a better harmonization of indications, image acquisition and interpretation. In these revised recommendations, we further simplified and shortened the brain MRI protocol for monitoring purposes, thereby making it easier and more likely to be used. We also recommend a re-baseline brain MRI scan (without Gd) 3-6 months after treatment initiation and annual follow-up scans after that also without Gd.

A novel recommendation compared to the previous guideline is to limit the repeated use of even macrocyclic GBCAs despite the lack of convincing clinical consequences. As GBCAs are not necessary in many clinical situations particularly during MS treatment monitoring, their judicious and limited use seems prudent. This can be achieved by obtaining more frequent unenhanced (re-baselining) scans.

We concluded that there is not enough evidence to recommend spinal cord MRI for routine follow-up monitoring of disease activity in MS on a regular basis, as it remains technically challenging and would increase the scanning time disproportionately. However, obtaining spinal cord MRI is important for diagnosis and when assessing the initial extent of CNS involvement (disease burden), and in other special

circumstances including unexplained and unexpected worsening and the possibility of an alternative diagnosis other than MS.

We have clarified that the recommendations for MRI in the diagnosis, prognosis, and monitoring of MS are equally applicable in most situations to both paediatric and adult-onset disease.

Finally, while 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 are high-resolution susceptibility-sensitive imaging for detecting the central vein sign and for 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 brain and spinal cord volume changes as helpful predictors of the evolution of MS and in monitoring the effects of MS treatment has been demonstrated 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.

Standardization and implementation of new and potentially more sensitive and specific imaging techniques represents one of our greatest challenges, but also one of our greatest opportunities, in the near future — particularly as new treatments focusing on neuroprotection, remyelination, and neuronal repair emerge.

References

1. Rovira À, Wattjes MP, Tintoré M, et al. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis-clinical implementation in the diagnostic process. *Nat Rev Neurol* 2015; 11:471-82.
2. Wattjes MP, Rovira À, Miller D, et al. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis--establishing disease prognosis and monitoring patients. *Nat Rev Neurol* 2015; 11:597-606.
3. Traboulsee A, Simon JH, Stone L, et al. Revised Recommendations of the Consortium of MS Centers Task Force for a Standardized MRI Protocol and Clinical Guidelines for the Diagnosis and Follow-Up of Multiple Sclerosis. *AJNR Am J Neuroradiol* 2016; 37:394-401.
4. Vågberg M, Axelsson M, Birgander R, et al. Guidelines for the use of magnetic resonance imaging in diagnosing and monitoring the treatment of multiple sclerosis: recommendations of the Swedish Multiple Sclerosis Association and the Swedish Neuroradiological Society. *Acta Neurol Scand* 2017; 135:17-24.
5. Yamout B, Alroughani R, Al-Jumah M, et al. Consensus recommendations for the diagnosis and treatment of multiple sclerosis: The Middle East North Africa Committee for Treatment and Research In Multiple Sclerosis (MENACTRIMS). *Curr Med Res Opin* 2015; 31:1349-61.
6. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17:162-173.
7. Gulani V, Calamante F, Shellock FG, et al. Gadolinium deposition in the brain: summary of evidence and recommendations. *Lancet Neurol* 2017; 16:564-570.
8. https://www.ema.europa.eu/en/medicines/human/referrals/gadolinium-containing-contrast-agents Assessed: 19 JUNE 2019
9. Arrambide G, Tintore M, Espejo C, et al. The value of oligoclonal bands in the multiple sclerosis diagnostic criteria. *Brain* 2018;141:1075-1084.
10. Geraldes R, Ciccarelli O, Barkhof F, et al. The current role of MRI in differentiating multiple sclerosis from its imaging mimics. *Nat Rev Neurol* 2018; 14:199-213.
11. Solomon AJ, Pettigrew R, Naismith RT, Chahin S, Krieger S, Weinshenker B. Challenges in multiple sclerosis diagnosis: Misunderstanding and misapplication of the McDonald criteria. *Mult Scler* 2020 Mar 12:1352458520910496. doi: 10.1177/1352458520910496. [Epub ahead of print]

12. Rotstein D, Montalban X. Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis. *Nat Rev Neurol* 2019;15:287-300.
13. Bose G, Freedman MS. Precision medicine in the multiple sclerosis clinic: Selecting the right patient for the right treatment. *Mult Scler* 2020;26:540-547.
14. Hu XY, Rajendran L, Lapointe E, et al. Three-dimensional MRI sequences in MS diagnosis and research. *Mult Scler* 2019 May 22:1352458519848100. doi: 10.1177/1352458519848100. [Epub ahead of print]
15. Hagens MH, Burggraaff J, Kilsdonk ID, et al. Impact of 3 Tesla MRI on interobserver agreement in clinically isolated syndrome: A MAGNIMS multicentre study. *Mult Scler* 2019; 25:352-360.
16. Hagens MHJ, Burggraaff J, Kilsdonk ID, et al. Three-Tesla MRI does not improve the diagnosis of multiple sclerosis: A multicenter study. *Neurology* 2018; 91:e249-e257.
17. Sati P. Diagnosis of multiple sclerosis through the lens of ultra-high-field MRI. *J Magn Reson* 2018; 291:101-109.
18. Maranzano J, Dadar M, Rudko DA, et al. Comparison of Multiple Sclerosis Cortical Lesion Types Detected by Multicontrast 3T and 7T MRI. *AJNR Am J Neuroradiol* 2019; 40:1162-1169.
19. Kilsdonk ID, Jonkman LE, Klaver R, et al. Increased cortical grey matter lesion detection in multiple sclerosis with 7 T MRI: a post-mortem verification study. *Brain* 2016; 139:1472-81.
20. van Waesberghe JH, Castelijns JA, Roser W, et al. Single-dose gadolinium with magnetization transfer versus triple-dose gadolinium in the MR detection of multiple sclerosis lesions. *AJNR Am J Neuroradiol* 1997; 18:1279-85.
21. Rovira A, Auger C, Huerga E, et al. Cumulative Dose of Macrocyclic Gadolinium-Based Contrast Agent Improves Detection of Enhancing Lesions in Patients with Multiple Sclerosis. *AJNR Am J Neuroradiol* 2017; 38:1486-1493.
22. Dekker I, Wattjes MP. Brain and Spinal Cord MR Imaging Features in Multiple Sclerosis and Variants. *Neuroimaging Clin N Am* 2017; 27:205-227.
23. Filippi M, Preziosa P, Banwell BL, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. *Brain* 2019; 142:1858-1875.
24. Bot JC, Barkhof F, Lycklama à Nijeholt G, et al. Differentiation of multiple sclerosis from other inflammatory disorders and cerebrovascular disease: value of spinal cord imaging. Radiology 2002; 223:46-56.
25. Wattjes MP, Steenwijk MD, Stangel M. MRI in the Diagnosis and Monitoring of Multiple Sclerosis: An Update. *Clin Neuroradiol* 2015;25 Suppl 2:157-65.

26. Philpott C, Brotchie P. Comparison of MRI sequences for evaluation of multiple sclerosis of the cervical spinal cord at 3 T. *Eur J Radiol* 201;80:780-5.
27. Bot JC, Barkhof F, Lycklama à Nijeholt GJ, et al. Comparison of a conventional cardiac-triggered dual spin-echo and a fast STIR sequence in detection of spinal cord lesions in multiple sclerosis. *Eur Radiol* 2000;10:753-8.
28. Ciccarelli O, Cohen JA, Reingold SC, et al. Spinal cord involvement in multiple sclerosis and neuromyelitis optica spectrum disorders. *Lancet Neurol* 2019; 18:185-197.
29. Nair, G., Absinta, M., Reich, D. Optimized T1-MPRAGE Sequence for Better Visualization of Spinal Cord Multiple Sclerosis Lesions at 3T *AJNR Am J Neuroradiol* 2013; 34, 2215-2222.
30. Mirafzal S, Goujon A, Deschamps R, et al. 3D PSIR MRI at 3 Tesla improves detection of spinal cord lesions in multiple sclerosis. *J Neurol* 2019 Oct 26. doi: 10.1007/s00415-019-09591-8. [Epub ahead of print]
31. Alcaide-Leon P, Pauranik A, Alshafai L, et al. Comparison of Sagittal FSE T2, STIR, and T1-Weighted Phase-Sensitive Inversion Recovery in the Detection of Spinal Cord Lesions in MS at 3T. *AJNR Am J Neuroradiol* 2016;37:970-5.
32. Moccia M, Ruggieri S, Ianniello A, Toosy A, Pozzilli C, Ciccarelli O. Advances in spinal cord imaging in multiple sclerosis. *Ther Adv Neurol Disord* 2019 Apr 22; 12:1756286419840593.
33. Kearney H, Miller DH, Ciccarelli O. Spinal cord MRI in multiple sclerosis--diagnostic, prognostic and clinical value. *Nat Rev Neurol* 2015; 11:327-38.
34. Weier K, Mazraeh J, Naegelin Y, et al. Biplanar MRI for the assessment of the spinal cord in multiple sclerosis. *Mult Scler* 2012; 18:1560-9.
35. Stankiewicz JM, Neema M, Alsop DC, et al. Spinal cord lesions and clinical status in multiple sclerosis: A 1.5 T and 3 T MRI study. *J Neurol Sci* 2009; 279:99-105.
36. Isaac C, Li DK, Genton M et al. Multiple sclerosis: a serial study using MRI in relapsing patients. *Neurology* 1988; 38:1511-5.
37. Edan G, Kappos L, Montalbán X, et al. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. *J Neurol Neurosurg Psychiatry* 2014;85:1183-1189.
38. Zecca C, Disanto G, Sormani MP, et al. Relevance of asymptomatic spinal MRI lesions in patients with multiple sclerosis. *Mult Scler* 2016; 22:782-91.
39. De Stefano N, Giorgio A, Tintoré M, et al. Radiologically isolated syndrome or subclinical multiple sclerosis: MAGNIMS consensus recommendations. *Mult Scler* 2018; 24:214-221.

40. Eisele P, Szabo K, Griebe M, et al. Reduced diffusion in a subset of acute MS lesions: a serial multiparametric MRI study. *AJNR Am J Neuroradiol* 2012; 33:1369-73.
41. Balashov KE, Lindzen E. Acute demyelinating lesions with restricted diffusion in multiple sclerosis. *Mult Scler* 2012; 18:1745-53.
42. Geurts JJ, Roosendaal SD, Calabrese M, et al. Consensus recommendations for MS cortical lesion scoring using double inversion recovery MRI. *Neurology* 2011; 76:418-24.
43. Sati P, George IC, Shea CD, Gaitán MI, Reich DS. FLAIR*: a combined MR contrast technique for visualizing white matter lesions and parenchymal veins. *Radiology* 2012 Dec;265(3):926-32.
44. Absinta M, Nair G, Monaco MCG, et al. The "central vein sign" in inflammatory demyelination: The role of fibrillar collagen type I. *Ann Neurol* 2019;85:934-942.
45. Cortese R, Magnollay L, Tur C, et al. Value of the central vein sign at 3T to differentiate MS from seropositive NMOSD. *Neurology* 2018; 90:e1183-e1190.
46. Maggi P, Absinta M, Grammatico M, et al. Central vein sign differentiates Multiple Sclerosis from central nervous system inflammatory vasculopathies. *Ann Neurol* 2018; 83:283-294.
47. Kilsdonk ID, Wattjes MP, Lopez-Soriano A, et al. Morphological features of MS lesions on FLAIR* at 7 T and their relation to patient characteristics. *Eur Radiol* 2014 ;24:841-9.
48. Sati P, Oh J, Constable RT, Evangelou N, et al. The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. *Nat Rev Neurol* 2016; 12:714-722.
49. Sinnecker T, Clarke MA, Meier D, et al. Evaluation of the Central Vein Sign as a Diagnostic Imaging Biomarker in Multiple Sclerosis. *JAMA Neurol* 2019 Aug 19. doi: 10.1001/jamaneurol.2019.2478. [Epub ahead of print]
50. Clarke MA, Pareto D, Pessini-Ferreira L, et al. Value of 3T susceptibility weighted imaging in the diagnosis of multiple sclerosis. *AJNR Am J Neuroradiol* 2020;41:1001-1008.
51. Maggi P, Sati P, Nair G, et al. Paramagenetic rim lesions are specific to multiple sclerosis: an international multicenter 3T MRI study. Ann Neurol 2020; Aug15. Doi10.1002/ana.25877. Online ahead of print.
52. Zurawski J, Lassmann H, Bakshi R. Use of Magnetic Resonance Imaging to Visualize Leptomeningeal Inflammation in Patients with Multiple Sclerosis: A Review. *JAMA Neurol* 2017; 74:100-109.
53. Absinta M, Vuolo L, Rao A, et al. Gadolinium-based MRI characterization of leptomeningeal inflammation in multiple sclerosis. *Neurology* 2015; 85:18-28.

54. Absinta M, Cortese IC, Vuolo L, et al. Leptomeningeal gadolinium enhancement across the spectrum of chronic neuroinflammatory diseases. *Neurology* 2017; 88:1439-1444.
55. Zivadinov R, Ramasamy DP, Hagemeier J, et al. Evaluation of Leptomeningeal Contrast Enhancement Using Pre-and Postcontrast Subtraction 3D-FLAIR Imaging in Multiple Sclerosis. *AJNR Am J Neuroradiol* 2018; 39:642-647.
56. Zivadinov R, Ramasamy DP, Vaneckova M, et al. Leptomeningeal contrast enhancement is associated with progression of cortical atrophy in MS: A retrospective, pilot, observational longitudinal study. *Mult Scler* 2017; 23:1336-1345.
57. Bergsland N, Ramasamy D, Tavazzi E, et al. Leptomeningeal Contrast Enhancement Is Related to Focal Cortical Thinning in Relapsing-Remitting Multiple Sclerosis: A Cross-Sectional MRI Study. *AJNR Am J Neuroradiol* 2019;4 0:620-625.
58. Ighani M, Jonas S, Izbudak I, et al. No association between cortical lesions and leptomeningeal enhancement on 7-Tesla MRI in multiple sclerosis. *Mult Scler* 2019 Oct 1:1352458519876037.
59. Petzold A, Wattjes MP, Costello F, et al. The investigation of acute optic neuritis: a review and proposed protocol. *Nat Rev Neurol* 2014; 10:447-58.
60. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol* 2016; 15:292-303.
61. Brownlee WJ, Miszkiel KA, Tur C, Barkhof F, Miller DH, Ciccarelli O. Inclusion of optic nerve involvement in dissemination in space criteria for multiple sclerosis. *Neurology* 2018;91:e1130-e1134.
62. Ramanathan S, Prelog K, Barnes EH, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. *Mult Scler* 2016;22:470-82.
63. Sastre-Garriga J, Pareto D, Battaglini M. et al. MAGNIMS consensus guidelines on the use of brain and spinal cord atrophy measures in clinical practice. *Nat Rev Neurol* 2020;16:171-182.
64. Enzinger C, Barkhof F, Ciccarelli O, et al. Nonconventional MRI and microstructural cerebral changes in multiple sclerosis. *Nat Rev Neurol* 2015; 11:676-86.
65. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018; 90:777-788.

66. Gasperini C, Prosperini L, Tintoré M, et al. Unraveling treatment response in multiple sclerosis: A clinical and MRI challenge. *Neurology* 2019; 92:180-192.
67. Wang KY, Uribe TA, Lincoln CM. Comparing lesion detection of infratentorial multiple sclerosis lesions between T2-weighted spin-echo, 2D-FLAIR, and 3D-FLAIR sequences. *Clin Imaging* 2018; 51:229–234.
68. Enzinger C, Barkhof F, Ciccarelli O, et al. Nonconventional MRI and microstructural cerebral changes in multiple sclerosis. *Nat Rev Neurol* 2015; 11:676-86.
69. Sastre-Garriga J, Pareto D, Battaglini M. et al. MAGNIMS consensus guidelines on the use of brain and spinal cord atrophy measures in clinical practice. *Nat Rev Neurol* 2020;16:171-182.
70. Gulani V, Calamante F, Shellock FG, et al. Gadolinium deposition in the brain: summary of evidence and recommendations. *Lancet Neurol* 2017; 16:564-570.
71. https://www.ema.europa.eu/en/medicines/human/referrals/gadolinium-containing-contrast-agents Assessed: 19 JUNE 2019
72. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-gadolinium-based-contrast-agents-gbcas-are-retained-body (assessed, April 12, 2020)
73. Traboulsee A, Li D. Addressing Concerns Regarding the Use of Gadolinium in a Standardized MRI Protocol for the Diagnosis and Follow-Up of Multiple Sclerosis. *AJNR Am J Neuroradiol* 2016;37:E82-E83.
74. Filippi M, Rossi P, Campi A, Colombo B, Pereira C, Comi G. Serial contrast-enhanced MR in patients with multiple sclerosis and varying levels of disability. *AJNR Am J Neuroradiol* 1997;18:1549-56.
75. Herranz E, Giannì C, Louapre C, et al. Neuroinflammatory component of gray matter pathology in multiple sclerosis. *Ann Neurol* 2016; 80:776-790.
76. Popescu BF, Frischer JM, Webb SM, et al. Pathogenic implications of distinct patterns of iron and zinc in chronic MS lesions. *Acta Neuropathol* 2017;134:45-64.
77. Elliott C, Wolinsky JS, Hauser SL, et al. Slowly expanding/evolving lesions as a magnetic resonance imaging marker of chronic active multiple sclerosis lesions. *Mult Scler* 2019; 25:1915-1925.
78. Filippi M, Preziosa P, Langdon D et al. Identifying progression in multiple sclerosis. *Ann Neurol* 2020;88:438-452.
79. Absinta M, Sati P, Masuzzo F, et al. Association of Chronic Active Multiple Sclerosis Lesions With Disability In Vivo. *JAMA Neurol* 2019 Aug 12. doi: 10.1001/jamaneurol.2019.2399. [Epub ahead of print]

80. Blindenbacher N, Brunner E, Asseyer S, et al. Evaluation of the 'ring sign' and the 'core sign' as a magnetic resonance imaging marker of disease activity and progression in clinically isolated syndrome and early multiple sclerosis. *Mult Scler J Exp Transl Clin* 2020;6:2055217320915480.
81. Nijeholt GJ, van Walderveen MA, Castelijns JA, et al. Brain and spinal cord abnormalities in multiple sclerosis. Correlation between MRI parameters, clinical subtypes and symptoms. *Brain* 1998;121:687-97.
82. Eichinger P, Schön S, Pongratz V, et al. Accuracy of Unenhanced MRI in the Detection of New Brain Lesions in Multiple Sclerosis. *Radiology* 2019; 291:429-435.
83. Pregliasco A, Collin A, Guéguen A, et al. Improved Detection of New MS Lesions during Follow-Up Using an Automated MR Coregistration-Fusion Method. *AJNR Am J Neuroradiol* 2018;39:1226-1232.
84. Magliozzi R, Howell O, Vora A, et al. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical atrophy. *Brain* 2007; 130:1089-104.
85. Mainero C, Louapre C, Govindarajan ST, et al. A gradient in cortical pathology in multiple sclerosis by in vivo quantitative 7 T imaging. *Brain* 2015;138:932-45.
86. Zecca C, Disanto G, Sormani MP, et al. Relevance of asymptomatic spinal MRI lesions in patients with multiple sclerosis. *Mult Scler* 2016; 22:782-91.
87. Eden D, Gros C, Badji A, et al. Spatial distribution of multiple sclerosis lesions in the cervical spinal cord. *Brain* 2019;142:633-646.
88. Signori A, Schiavetti I, Gallo F, Sormani MP. Subgroups of multiple sclerosis patients with larger treatment benefits: a meta-analysis of randomized trials. *Eur J Neurol* 2015; 22:960-6.
89. Río J, Rovira À, Tintoré M, et al. Disability progression markers over 6-12 years in interferon-β-treated multiple sclerosis patients. *Mult Scler* 2018; 24:322-330.
90. Bovis F, Carmisciano L, Signori A, et al. Defining responders to therapies by a statistical modeling approach applied to randomized clinical trial data. *BMC Medicine* 2019; 17:113. doi: 10.1186/s12916-019-1345-2.
91. Marta M, Giovannoni G. Disease modifying drugs in multiple sclerosis: mechanisms of action and new drugs in the horizon. *CNS Neurol Disord Drug Targets* 2012;11: 610–623.

92. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. *Ann Neurol* 2001; 49:290-7.
93. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. *Neurology* 2012;78:1069-78.
94. Río J, Auger C, Rovira. MR Imaging in Monitoring and Predicting Treatment Response in Multiple Sclerosis. *Neuroimaging Clin N Am* 2017;27:277-287.
95. Sormani MP, De Stefano N. Defining and scoring response to IFN-β in multiple sclerosis. *Nat Rev Neurol* 2013; 9:504-512.
96. Grebenciucova E, Pruitt A. Infections in Patients Receiving Multiple Sclerosis Disease-Modifying Therapies. *Curr Neurol Neurosci Rep* 2017; 17:88.
97. Marrie RA. Comorbidity in multiple sclerosis: implications for patient care. *Nat Rev Neurol* 2017; 13:375-382.
98. Thormann A, Magyari M, Koch-Henriksen N, Laursen B, Sørensen PS. Vascular comorbidities in multiple sclerosis: a nationwide study from Denmark. *J Neurol* 2016; 263:2484-2493.
99. Smith KA, Burkill S, Hiyoshi A, et al. Comorbid disease burden among MS patients 1968-2012: A Swedish register-based cohort study. *Mult Scler* 2020 Mar 12:1352458520910497. doi: 10.1177/1352458520910497. [Epub ahead of print]
100. Diebold M, Altersberger V, Décard BF, et al. A case of progressive multifocal leukoencephalopathy under dimethyl fumarate treatment without severe lymphopenia or immunosenescence. *Mult Scler* 2019; 25:1682-1685.
101. Nakahara J, Tomaske L, Kume K, et al. Three cases of non-carryover fingolimod-PML: Is the risk in Japan increased? *Neurol Neuroimmunol Neuroinflamm* 2019 Apr 10;6(3):e559.
102. Gerevini S, Capra R, Bertoli D, Sottini A, Imberti L. Immune profiling of a patient with alemtuzumab-associated progressive multifocal leukoencephalopathy. *Mult Scler* 2019;25:1196-1201.
103. https://multiple-sclerosis-research.org/2019/10/de-novo-pml-on-ocrelizumab/ Accessed: 23 October 2019
104. Dong-Si T, Richman S, Wattjes MP, et al. Outcome and survival of asymptomatic PML in natalizumab-treated MS patients. *Ann Clin Transl Neurol* 2014; 1:755-64.

105. Ho PR, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. *Lancet Neurol* 2017;16:925-933.

106. McGuigan C, Craner M, Guadagno J, et al. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J Neurol Neurosurg Psychiatry 2016;87:117-25.

107. Scarpazza C, Signori A, Cosottini M, Sormani MP, Gerevini S, Capra R. Should frequent MRI monitoring be performed in natalizumab-treated MS patients? A contribution to a recent debate. *Mult Scler* 2019 May 30:1352458519854162.

108. Ryerson LZ, Foley J, Chang I, et al. Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing. *Neurology* 2019;93:e1452-e1462.

109. Wijburg MT, Warnke C, Barkhof F, Uitdehaag BMJ, Killestein J, Wattjes MP. Performance of PML diagnostic criteria in natalizumab-associated PML: data from the Dutch-Belgian cohort. *J Neurol Neurosurg Psychiatry* 2019; 90:44-46.

110. Wijburg MT, Kleerekooper I, Lissenberg-Witte BI, et al. Association of Progressive Multifocal Leukoencephalopathy Lesion Volume with JC Virus Polymerase Chain Reaction Results in Cerebrospinal Fluid of Natalizumab-Treated Patients with Multiple Sclerosis. *JAMA Neurol* 2018; 75:827-833.

111. Wijburg MT, Witte BI, Vennegoor A, et al. MRI criteria differentiating asymptomatic PML from new MS lesions during natalizumab pharmacovigilance. *J Neurol Neurosurg Psychiatry* 2016; 87:1138-45.

112. Wattjes MP, Wijburg MT, Vennegoor A, et al. MRI characteristics of early PML-IRIS after natalizumab treatment in patients with MS. *J Neurol Neurosurg Psychiatry* 2016;87:879-84.

113. Scarpazza C, Signori A, Prosperini L, et al. Early diagnosis of progressive multifocal leucoencephalopathy: longitudinal lesion evolution. *J Neurol Neurosurg Psychiatry* 2019; 90:261-267.

114. Fadda G, Brown RA, Longoni G, et al. MRI and laboratory features and the performance of international criteria in the diagnosis of multiple sclerosis in children and adolescents: a prospective cohort study. *Lancet Child Adolesc Health* 2018;2:191-204.

115. Waldman A, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M, Banwell B. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. *Lancet Neurol* 2014;13:936-48.

116. Chitnis T, Glanz B, Jaffin S, Healy B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. *Mult Scler* 2009;15:627-631.

117. Ramanathan S, Prelog K, Barnes EH, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. *Mult Scler* 2016; 22:470-482.

118. Hummel HM, Brück W, Dreha-Kulaczewski S, Gärtner J, Wuerfel J.Pediatric onset multiple sclerosis: McDonald criteria 2010 and the contribution of spinal cord MRI. *Mult Scler* 2013;19:1330-5.

119. O'Mahony J, Bar-Or A, Arnold DL, et al. Masquerades of acquired demyelination in children: experiences of a national demyelinating disease program. *J Child Neurol* 2013;28:184-97.

120. Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. *Neurology* 2009; 72:750-759.

121. Verhey LH, Signori A, Arnold DL, et al. Clinical and MRI activity as determinants of sample size for pediatric multiple sclerosis trials. *Neurology* 2013;81:1215-21

122. Aubert-Broche B, Fonov V, Narayanan S, et al. Onset of multiple sclerosis before adulthood leads to failure of age-expected brain growth. *Neurology* 2014;83:2140-6.

123. Arnold DL, Banwell B, Bar-Or A, et al. Effect of fingolimod on MRI outcomes in patients with paediatric-onset multiple sclerosis: results from the phase 3 PARADIGMS study. *J Neurol Neurosurg Psychiatry* 2020;91:483-492.

124. Bulas D, Egloff A. Benefits and risks of MRI in pregnancy. *Semin Perinatol* 2013; 37:301-304.

125. Chen MM, Coakley FV, Kaimal A, Laros RK Jr. Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. *Obstet Gynecol* 2008; 112:333-40.

126. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes. *JAMA* 2016; 316:952-61.

127. Barrera CA, Francavilla ML, Serai SD, et al. Specific Absorption Rate and Specific Energy Dose: Comparison of 1.5-T versus 3.0-T Fetal MRI. *Radiology* 2020:191550.

128. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Maternal fever and birth outcome: a prospective study. *Teratology* 1998; 58:251-7.

129. Moretti ME, Bar-Oz B, Fried S, Koren G. Maternal hyperthermia and the risk for neural tube defects in offspring: systematic review and meta-analysis. *Epidemiology* 2005;16:216-9.

130. Novak Z, Thurmond AS, Ross PL, Jones MK, Thornburg KL, Katzberg RW. Gadolinium-DTPA transplacental transfer and distribution in fetal tissue in rabbits. *Invest Radiol* 1993;28:828-30.

131. Bsteh G, Algrang L, Hegen H, et al. Pregnancy and multiple sclerosis in the DMT era: A cohort study in Western Austria. *Mult Scler* 2018 Dec 3:1352458518816614.

132. Sundgren PC, Leander P. Is administration of gadolinium-based contrast media to pregnant women and small children justified? *J Magn Reson Imaging* 2011;34:750-7.

133. ESUR Guidelines on Contrast Agents. European Society of Urogenital Radiology. V10. March 2018. http://www.esur.org/fileadmin/content/2019/ESUR_Guidelines_10.0_Final_Version.pdf Accessed: 23 March 2020

Table 1. Basic MRI Parameters

	Brain	Spinal cord	Optic nerve
Field strength	≥1.5T[1]	≥1.5T[2]	≥1.5T
Slice thickness	3D: 1mm isotropic (preferred); if overcontiguous (through-plane and in-plane), not > 1.5mm and 0.75 mm overlap 2D: ≤ 3 mm, no gap[3]	Sagittal ≤ 3 mm, no gap Axial ≤ 5 mm, no gap	≤ 2-3 mm, no gap
In-plane resolution	≤ 1mm x 1mm	≤ 1mm x 1mm	≤ 1mm x 1mm
Coverage	Whole brain (include as much of cervical cord as possible)	Cervical Thoracolumbar, to include conus	Optic nerve and optic chiasm
Axial scan orientation	Subcallosal plane to prescribe (2D) or reformat (3D) axial oblique slices	Perpendicular to the sagittal axis of the spinal cord	Aligned to the orientation of the optic nerve and optic chi-asm

Abbreviations: D=dimensional, T=tesla

[1] preferably 3T; [2] 3T has no added value compared to 1.5T; [3] except for DWI, which should be ≤ 5 mm

Table 2. Standardized brain MRI protocol

	MS diagnosis	Assessment of disease activity and DMT efficacy monitoring	DMT safety monitoring[1]
Axial T2w (TSE/FSE)[2]	recommended	recommended[3]	recommended[3]
Sagittal T2w FLAIR (preferably 3D)[4]	recommended	recommended	recommended
Axial T2w FLAIR[4,5]	recommended	recommended	optional
Axial (or 3D sagittal) T1w-post contrast[6]	recommended	optional	optional
DWI	optional[7]	optional[7]	recommended
DIR/PSIR[8]	optional	optional	optional
High resolution T1w[9]	optional	optional	not required
SWI	optional[10]	not required	not required
Axial and coronal FS T2w or STIR optic nerve	optional[11]	not required	not required
Axial and coronal FS T1w post contrast optic nerve	optional[11]	not required	not required

[1]the term safety monitoring refers to PML screening

[2] a dual echo (proton density and T2w) sequence can be considered as an alternative to a single echo T2w sequence

[3] optional: in the case of the availability of high-quality 3D T2w-FLAIR and multiplanar reconstructions in axial and sagittal plane.
[4] fat suppression optional
[5] unnecessary if a sagittal 3D FLAIR with multiplanar reconstruction is obtained
[6] standard doses of 0.1 mmol/kg bodyweight, macrocyclic gadolinium chelates only, with a minimum delay of 5-7 minutes
[7] DWI should be considered for differential diagnosis purposes
[8] for detecting cortical/juxtacortical lesions
[9] isotropic 3D acquisition. For quantitative assessment of brain volume
[10] for assessing the "central vein sign"
[11] can be considered in certain clinical situations as summarized in Table 4. Can be either 2D or 3D acquisition

MS=multiple sclerosis, DMT=disease modifying treatment, (TSE/FSE)=turbo spin echo/fast spin echo, FLAIR=fluid attenuated inversion recovery, DIR=double inversion recovery, PSIR=phase-sensitive inversion recovery, DWI=diffusion weighted imaging, FS=fat suppressed

Table 3: Standardized spinal cord MRI protocol

	MS diagnosis	Efficacy monitoring and assessment of disease activity in patients not treated [5]
Sagittal T2 (TSE/FSE) / PD(TSE/FSE) / STIR[1]	recommended	optional
Sagittal 3D heavily T1w (PSIR or MPRAGE)[2]	optional	optional
Axial T2w (TSE/FSE) or GRE[3]	optional	optional
Sagittal T1w (TSE/FSE) pre contrast	optional	optional
Sagittal T1w (TSE/FSE) post contrast[4]	recommended	optional
Axial T1w (TSE/FSE) post contrast[4]	optional	optional

[1] At least two out of these three sequences
[2] Only for the cervical segment. One of these sequences could replace T2, PD, or STIR
[3] To corroborate, characterize and confirm lesions detected on sagittal images, or to detect lesions in spinal cord segments with high clinical suspicious of involvement
[4] Standard doses of 0.1 mmol/kg bodyweight, macrocyclic gadolinium chelates only. No additional gadolinium necessary if cord examination immediately follows gadolinium enhanced brain MRI
[5] Spinal cord MRI for assessing treatment efficacy and monitoring disease activity is not recommended on regular basis but is advised for special clinical conditions only (see Table 4).

MS=multiple sclerosis, (TSE/FSE)=turbo spin echo/fast spin echo, PD=proton density, STIR=short tau inversion recovery, PSIR=phase sensitive inversion recovery, MPRAGE=magnetization prepared rapid acquisition of gradient echoes, GRE=gradient recalled echo

Table 4. Indications to use spinal cord imaging for diagnosis, prognosis, and monitoring

Clinical situation	Indication and objective
Diagnosis	• CIS: establishing the diagnosis according to McDonald criteria - detection of symptomatic / asymptomatic spinal cord lesions to demonstrate dissemination in space and time • CIS: differential diagnosis in case of inconclusive brain MRI findings - presence of typical demyelinating spinal cord lesions - differential diagnosis, including NMOSD and MOG antibody disease • Primary progressive MS: establishing the diagnosis - detection of typical demyelinating spinal cord lesions to demonstrate dissemination in space - detection of diffuse demyelination (diffuse abnormal white matter, DAWM) - exclusion of alternative diagnosis (e.g., compressive myelopathy)
Prognosis	• RIS: prediction of CIS/MS development - detection of asymptomatic spinal cord lesions • CIS/early MS: prediction of disability, disability progression, and development of SPMS - detection of spinal cord lesions (active lesions in follow-up MRIs)
Monitoring	• MS patients with spinal cord phenotype (no or low number of brain lesions) - detection of active spinal cord lesions • MS patients with clinical disease progression that cannot be explained by brain MRI - detection of active spinal cord lesions - exclusion of possible comorbidity involving the spine/spinal cord • MS patients with (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 and/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 suggestive of comorbidity - detection of active spinal cord lesions - exclusion of alternative diagnosis or possible comorbidity involving the spinal cord

CIS=clinically isolated syndrome, MS=multiple sclerosis, RIS=radiologically isolated syndrome, SPMS=secondary progressive MS, MRI=magnetic resonance imaging, NMOSD=neuromyelitis optica spectrum disorders, MOG= Myelin oligodendrocyte glycoprotein

Table 5. Recommendations on the use of GBCAs in the diagnosis and monitoring of MS

Clinical situation	Indication and objective
Diagnosis	**The use of GBCAs is recommended** • To demonstrate dissemination in time on the baseline MRI scan • To contribute to differential diagnosis (based on the pattern of enhancement) • To predict disability progression • For phenotyping progressive patients (active/inactive), if a recent (one year) MRI is not available, and if this information impacts treatment decisions
Monitoring	**The use of GBCAs is recommended** • First year follow-up (after treatment onset) if a re-baseline MRI was not obtained particularly in patients receiving injectables • If detecting or confirming recent clinical disease activity is required in patients without a recent reference brain MRI (performed ≤ 3-6 months). MRI should be ideally performed as soon as possible and before steroid treatment. • If demonstration of recent disease activity based on presence of Gd enhancing lesions is required to initiate or change a specific disease modifying treatment • In patients with diffuse and confluent chronic MS lesions (large lesion burden), in which detection of disease activity based is required but difficult to achieve based on new/enlarged T2 lesions • For PML screening if there has been a suspicious lesion detected on the standard monitoring/screening brain MRI scan **The use of GBCAs is not recommended** • To demonstrate DIT on serial MRI scans • In case of standard monitoring purposes for subclinical disease activity, if comparable previous and relatively recent (approximately one year) MRI scan is available • In re-baseline MRI scans • In shorter follow-up MRI (6 months) performed to confirm disease activity in patients with isolated MRI activity on the previous MRI • For PML screening • During pregnancy (strictly contraindicated) and lactation (relative contraindicated)

GBCAs=gadolinium-based contrast agents, MS=multiple sclerosis, PML=progressive multifocal leukoencephalopathy

Table 6. Indications to use optic nerve MRI for diagnosis and monitoring of disease activity

Clinical situation	Indication and objective
Diagnosis	• CIS: differential diagnosis in case of suspected: - Atypical isolated optic neuritis; relapsing isolated optic neuritis; chronic relapsing inflammatory optic neuropathy - Other diseases affecting the optic nerve: NMOSD, infectious diseases, post vaccination, sarcoidosis, tumours, etc. - Optic neuritis in paediatric patients
Monitoring	• MS patients with new visual symptoms suggestive of comorbidity affecting the optic nerve • MS patients with chronic progressive optic nerve symptoms • MS patients with repeated isolated optic nerve relapses

CIS=clinically isolated syndrome, MS=multiple sclerosis, NMOSD=neuromyelitis optica spectrum disorder

Figure legends

Figure 1. Recommended brain MRI protocol

Footnotes

Resolution: 3D sequences: 1x1x1mm (multiplanar reconstruction 3mm); 2D sequences: 1x1x3mm

[a] Either single or dual echo.

[b] Can be skipped in case of good quality 3D FLAIR in the monitoring protocol

[c] For differential diagnosis

[d] Transverse 2D FLAIR could be considered as an alternative, if 3D-FLAIR not available or not of good quality

Abbreviations: TSE, turbo spin echo; CE, contrast enhanced; DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; Gd, gadolinium; BW, body weight;

Figure 2. Recommended spinal cord MRI protocol

Footnotes:

[a]Select PD or STIR

[b]Only in selected cases, and if possible after acquisition of the CE brain MRI (in this case this sequence should be acquired first) (minimum delay 5-10 minutes)

[c]Only in selected cases

Abbreviations: CE, contrast enhanced; Gd, gadolinium; STIR, short tau inversion recovery; TSE, turbo spin echo; PD, proton density

Figure 3. Computer-assisted-detection of active T2 lesions. 3D FLAIR images obtained at baseline (A) and one year after (B). The co-registered and subtracted image (C) shows four new T2 lesions depicted as white dots (arrows), all of them confirmed on visual analysis of the 3D FLAIR images.

Figure 4. MRI timing in monitoring MS

Footnotes

a Shorter follow-up MRI (6 months) if isolated significantly MRI activity or isolated clinical activity

b Add spinal cord MRI to brain MRI if clinically indicated

c Add spinal cord MRI to brain MRI if never performed;

d Longer intervals to be considered in patients treated with certain DMTs

e Less frequent MRIs in clinically stable patients treated with IFN or GA

f Consider Gd administration in patients with highly active disease at baseline or in patients with unexpected clinical activity after treatment initiation

g Consider Gd in patients receiving moderate efficacy DMTs if re-baseline MRI not performed

Abbreviations: DMT, disease-modifying treatment; GA, glatiramer acetate; IFN, interferon; Gd, gadolinium

Figure 5. Abbreviated brain MRI protocol for PML screening (observe a small asymptomatic PML lesion in the right prerolandic juxtacortical white matter) (arrows)

Footnotes

Resolution: 3D sequences: 1x1x1mm (multiplanar reconstruction 3mm); 2D sequences: 1x1x3mm

[a] Transverse 2D FLAIR could be considered as an alternative, if 3D-FLAIR not available or not of good quality

Abbreviations: TSE, turbo spin echo; DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery.