MRI CRITERIA FOR THE DIAGNOSIS OF MULTIPLE SCLEROSIS: THE 2015 MAGNIMS REVISION

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Summary

The available MRI diagnostic criteria in patients with multiple sclerosis (MS) need clarifications and modifications. Within the MAGNIMS network, a workshop was held to discuss the state-of-the-art MRI findings in these patients and provide an evidence-based and expert opinion consensus on how the diagnostic algorithm should be modified. Proposed modifications to disease dissemination in space (DIS) criteria include: increasing the number of lesions necessary to confirm the involvement of the periventricular area, from 1 to 3; adding the optic nerve as an additional CNS location; using the term "cortical/juxtacortical" to expand the concept of juxtacortical lesions. Apply identical DIS criteria for progressive- and relapse-onset MS. No distinction should be made between symptomatic and asymptomatic lesions. Similar MRI criteria should be applied to: a) children with non-ADEM-like presentation; b) Asia or Latin America populations; and c) radiologically isolated syndrome subjects. Lesion features distinctive of MS could emerge from the use of ultra-high field scanners.

Key words: Multiple Sclerosis; Magnetic Resonance Imaging; Diagnosis; Criteria.

Introduction

Magnetic resonance imaging (MRI) has been formally included in the diagnostic work-up of patients presenting with a clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS) in 2001 by an International Panel of experts.[1] MS diagnosis requires the demonstration of disease dissemination in space (DIS) and time (DIT) and the exclusion of other conditions that can mimic MS by their clinical and laboratory profile. MRI can support and substitute clinical information for MS diagnosis, allowing an earlier and accurate diagnosis and, consequently, earlier treatment.

MRI criteria for MS are based on the presence of focal lesions in the white matter (WM) of the central nervous system (CNS), which are considered typical for this condition in terms of distribution, morphology, evolution and signal abnormalities on conventional MRI sequences (e.g., T2-weighted, T2-FLAIR, pre- and post-contrast T1-weighted scans).[2-4] Several modifications of MRI diagnostic criteria have been proposed over the years. These revisions have simplified the lesion count models for demonstrating DIS, changed the timing of MRI scan for demonstrating DIT, and increased the value of spinal cord imaging.[5-8] In 2007 the European collaborative research network that studies MRI in MS (MAGNIMS) has reviewed the findings of studies that addressed these issues and proposed new MRI criteria to be applied in MS.[9] Those MAGNIMS criteria are currently included in the most recent of the MS diagnostic criteria, known as the 2010 McDonald criteria.[10] Recent consensus guidelines for clinicians for the optimization of the use of brain and spinal cord MRI in the diagnostic process of MS (planning, performance and interpretation) have also been published.{Rovira, 2015 #2455}

Since 2011, new data regarding the application of MRI for demonstrating DIS and DIT have become available, and these deserve consideration for future revisions of the MS criteria. Additionally, many improvements in MRI technology have occurred, which resulted in the development of innovative acquisition sequences, the identification of novel pathophysiological mechanisms which may help in the differential diagnosis, as well as new insights into MS disease activity as evidenced by high field and ultra-high field scanners. Within MAGNIMS, it was felt that

there is the need of a timely revision of these recent findings and how these should modify the diagnostic work-up of MS patients.

Methods

In March 2015, an international workshop was held in Milan, Italy, under the auspices of MAGNIMS. The workshop involved clinical and imaging experts in the diagnosis and management of patients with MS, and included physicians, neurologists and neuroradiologists. Before the meeting, two co-chairs (MF and FB) identified topics that were deemed to need a revision and/or a definition in future MS diagnostic criteria. Experts for each topic were invited to provide a summary during the meeting of the main findings related to their argument, based on revision of the literature and on their personal experience. Afterwards, they had to define whether such a measure was judged useful or not in the diagnostic process and whether it was promising to move the field forward in the future, in order to stimulate group discussion. For each measure, a group agreement was reached during the workshop, and summarized in a first draft, which was circulated among the meeting participants plus some additional experts in the field for critical discussion and revision.

MRI criteria for DIS

According to the 2010 McDonald criteria for MS,[10] DIS can be demonstrated with at least one T2 lesion in at least 2 of 4 locations characteristic for MS (juxtacortical, periventricular, infratentorial, and spinal cord). We propose to increase the number of lesions necessary to confirm the involvement of the periventricular area, from 1 to 3, and add an additional CNS location, which is the optic nerve (Table 1).

Periventricular lesions. A single lesion was deemed not sufficiently sensitive to define whether the involvement of the periventricular region is due to a demyelinating inflammatory event. Indeed, incidental periventricular lesions can be detected in healthy individuals and patients with other neurological conditions, including up to 30% of patients with migraine.[11] The analysis of a

large cohort of 652 CIS patients has shown that in patients not satisfying DIS criteria for MS, the presence of 3 periventricular lesions, combined with age or presence of oligoclonal bands (OB), is helpful in identifying those at risk for MS.[12] In a retrospective study in patients with spinal cord CIS, a prediction model, including age $\leq$40 years, $\geq$3 periventricular lesions, and immunoglobulin intrathecal synthesis identified with an accuracy of 78% patients evolving to MS.[13] Interestingly, $\geq$3 periventricular lesions was the most accurate threshold determined by receiver-operating curve analysis in Barkhof et al.[4] and applied in previous McDonald criteria.[1, 8] In a multicenter trial of 468 CIS patients, the presence of at least 3 periventricular lesions had a strong prognostic value for conversion to MS over a 3 year period.{Moraal, 2009 #2457} In a study comparing patients with MS and those with from primary and secondary CNS vasculitis, the presence of $\geq$3 periventricular lesions was the only individual components of the Barkhof's criteria able to distinguish MS from SLE/Sjogren's patients.{Kim, 2014 #2456}

In pediatric MS patients, however, the presence of a single periventricular lesion (as well as one or more T1 hypointense lesions) powerfully distinguished children with MS from children with monophasic demyelination.[14]

Optic nerve lesions. Around 20-31% of CIS patients present with an acute optic neuritis.[15-17] Compared to other clinical presentations, adult patients with optic neuritis are more likely than those with acute demyelination in other CNS locations to have a monophasic illness,[15, 18, 19] as also confirmed by a recent study that enrolled 1058 CIS patients.[16] Importantly, in this cohort and in other studies, the likelihood of optic neuritis being a monophasic illness is dramatically reduced if the presence of CSF OB and/or the presence of clinically silent brain MRI lesions (with a hazard ratio [HR] of 5.1 for patients with one to three lesions, and 11.3 for patients with 10 or more lesions). The presence of even one clinically silent T2 hyperintense brain lesion in children with optic neuritis is highly associated with confirmation of a MS diagnosis,[20] while the absence of brain lesions is strongly predictive of a monophasic illness.[21]

Clinical features of optic neuritis (visual impairment, scotoma, red-green desaturation, pain with ocular movement), MRI evidence of optic nerve inflammation (increased T2 signal, gadolinium enhancement or optic nerve swelling), and neurophysiological test (visual evoked potentials or optical coherence tomography) supports the optic nerve as an additional CNS area affected at CIS onset. Clinical documentation of optic nerve atrophy or pallor, neurophysiological confirmation of optic nerve dysfunction (slowed conduction, and retinal nerve fiber layer thinning), or MRI features of clinically silent optic nerve inflammation support DIS, and in patients without concurrent visual symptoms, also support DIT.

Cortical lesions. Pathologic studies have shown extensive involvement of the gray matter (GM) in MS patients.[22-24] According to their location within the GM, different cortical lesion (CL) locations (sub-pial, purely intracortical, and leukocortical lesions abutting the GM-WM border) have been identified.[23] Imaging CL is challenging (particularly using conventional clinical scan protocols). Different MRI techniques have been proposed and are currently being compared for their sensitivity to CL detection, including double inversion recovery (DIR),[25] phase-sensitive inversion recovery (PSIR)[26-28] and magnetization-prepared rapid acquisition with gradient echo[29] sequences (Figure 1). Despite this, correlative MRI-pathology studies have shown that many CLs remain invisible on MRI, at least at 1.5 and 3.0 Tesla MRI strengths.[30, 31]

Using DIR sequences, CLs have been identified in more than 30% of CIS patients.[32, 33] In a cohort of 80 CIS patients with a 4-year follow up, the accuracy of MRI diagnostic criteria for MS was increased when considering the presence of at least 1 intracortical (IC) lesion on baseline scans.[33] CL assessment may also help in the differential diagnosis between MS and mimicking-MS conditions, since they have not been found in patients with migraine with T2-WM lesions[11] or neuromyelitis optica (NMO).[34] IC lesions are also rare in healthy controls (1/60 subjects using PSIR sequences).[27]

Even with these promising results, there remain many unsolved issues related to the inclusion of CL assessment in the diagnostic work-up of CIS patients. First, the MRI sequences

used in research setting for the identification of these lesions may not be available and easily implementable on the majority of clinical scanners. Second, the acquisition parameters for these sequences still need to be standardized on different manufactures and field strengths. Third, inter-observer agreement in the assessment of these sequences is moderate (complete agreement=19% for DIR), and guidelines for their evaluation are evolving.[27, 35] Fourth, different criteria and terms are currently being applied by different research groups for the distinction between IC, leukocortical, mixed WM/GM and juxtacortical lesions.[25-28, 33] Additionally, subpial demyelination, which can be quite extensive, is usually not scored.[24] The term "cortical/juxtacortical" is recommended to expand the concept of juxtacortical lesion in the DIS criteria and to include all types of MS CLs.

MRI criteria for DIT

According to the 2010 McDonald criteria,[10] DIT can be demonstrated by: 1) a new T2 and/or gadolinium-enhancing lesion(s) on follow up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI, or 2) the simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time.

<u>Non-enhancing T1-hypointense lesions (black holes)</u>. Non-enhancing T1-hypointense lesions (black holes) are chronic lesions characterized by severe axonal damage.[36] In relapsing-remitting (RR) MS, brain T1-hypointense lesion volume increases by approximately 11% per year and correlates with long-term disability progression.[37, 38] T1-hypointense lesion formation is more common in patients with longer disease durations and progressive disease subtypes. For that reason, their presence in CIS patients is indicative of an already established MS disease process. The prevalence of non-enhancing T1-hypointense lesions and their added value in identifying adult patients with MS was analyzed in a large multicenter study of 520 CIS patients.[39] Non-enhancing black holes were relatively common in adult CIS patients (36%) and were associated with a higher likelihood of MS diagnosis. However, the value of this MR finding for predicting a second clinical attack in these patients was last when added to the other criteria.[39] Of note, T1-hypointese lesion

assessment is still rather subjective and highly dependent on the type of T1-weighted sequence and field strength. Nevertheless, in pediatric patients with acute demyelination, the presence of one or more T1 hypointense lesion was highly correlated with subsequent confirmation of MS.[14]

Symptomatic lesions

In CIS patients, the symptomatic lesions that align with the acute clinical deficit(s) do not contribute to the DIS or DIT component of the MS diagnostic criteria.[10] Specifically, in patients with brainstem or spinal cord syndromes, lesions within the symptomatic region cannot be counted for demonstration of DIS. The simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time is a criterion to define DIT.

In CIS patients presenting with brainstem symptoms, a 2004 study showed that the specificity for MRI criteria for DIS (Barkhof's criteria at that time) was lower (61%) than that found in other CIS (myelitis and optic neuritis) (73%).[40] A recent investigation[41] assessed the likelihood of MS confirmation in 35/954 patients (3%) with one single symptomatic lesion of the brainstem or spinal cord with a follow up of almost 8 years. The HR of MS was higher for patients with a symptomatic lesion (HR=7.2) than for those with a single asymptomatic lesion in the same regions (HR=5.7) or no lesions (HR=1). Another retrospective study in 146 CIS patients who fulfilled the 2010 McDonald criteria[10] found that the presence of a symptomatic lesion identifies with a high sensitivity those patients with MS.[42] In a recent study of 30 CIS patients who were studied for a mean of 7.3 years after onset, the sensitivity/specificity/accuracy of the DIS criteria was 73/73/73% for the 2010 McDonald criteria, 80/73/77% when asymptomatic lesions in the symptomatic region were included and 87/73/80% when any lesion in the symptomatic region was included in DIS.{Brownlee, 2015 #2458} This suggests that including lesions in the symptomatic region in DIS may increase the sensitivity of MRI criteria for diagnosing MS without compromising specificity.

The diagnostic impact of allowing any gadolinium-enhancing and non-enhancing lesions (not only asymptomatic, but also symptomatic lesions) to count for demonstrating DIT has also been recently analyzed.[43] Inclusion of symptomatic lesions in the DIT criteria increased the proportion of patients satisfying the MRI diagnostic criteria for MS to 33%, compared to 30% of those diagnosed without including such lesions, with three additional patients meeting the 2010 McDonald criteria. In fact, deciding what is symptomatic or not is often very difficult. It is easier to apply in brainstem/spinal cord presentation but no other clinical scenario.

Spinal cord imaging

Based on the 2010 McDonald criteria,[10] clinically-silent spinal cord lesions can contribute to both DIS and DIT. At symptom onset, spinal cord imaging is recommended in patients with clinical features localized to the spinal cord to rule out alternative cord pathology (i.e., compression, spinal cord tumor, NMO, vasculitides, etc.) and in those with non-spinal CIS not fulfilling brain MRI for DIS. In this second group, whole cord imaging showed that the presence of one spinal cord lesion identifies patients at higher risk of MS confirmation.[44] Imaging of the entire cord, using at least two MR sequences (e.g., T2 and STIR, T2 and DIR, T2 and post-contrast T1-weighted scan, etc.) is preferable to increase confidence in lesion identification, in part because approximately 40% of spinal cord lesions are found in the thoraco-lumbar region (Figure 2).[45-47] The value of spinal cord imaging for DIT in patients without accrual of deficits referable to the spine is limited, since new clinically silent cord lesions are not frequent.

Primary progressive MS

In the different formulations of the diagnostic criteria, the diagnosis of primary progressive (PP) MS has always been kept separate from that of the more common relapse-onset form of the disease. In 2009, there was a proposal of unification of DIS MRI criteria for PPMS and relapsing-MS[48] which was only partially integrated in the 2010 McDonald criteria.[10] Indeed, according to

these criteria, DIS in PPMS was defined by the occurrence of two of the following three criteria: 1) DIS in the brain, based on the presence of at least one lesion in at least one area characteristic for MS (periventricular, juxtacortical or infratentorial); 2) DIS in the spinal cord, based on the presence of at least two lesions in the spinal cord; and 3) positive CSF examination.

The sensitivity of the spinal cord criteria and the utility of CSF examination has been retrospectively analyzed in a cohort of 95 PPMS patients.[49] These authors found that if the requirement for two or more cord lesions was changed to one or more cord lesions (whether symptomatic or not), a higher number of patients would meet the spinal cord criteria for diagnosis, with increasing sensitivity and simplification of the criteria. Specificity of these criteria has still to be tested.

MRI criteria in pediatric populations

The 2010 consensus was that the proposed MRI criteria also served for most pediatric MS patients. An alert was specified that the use of the 2010 McDonald criteria for MS at baseline was not applicable for children with encephalopathy and multifocal neurological deficits meeting criteria for ADEM.[10] Such children have multiple lesions, some of which may enhance, yet when defined using international consensus criteria for ADEM, 95% of such children have a monophasic illness.[21] The diagnosis of MS in pediatric patients manifesting initially with an ADEM-like first attack requires clinical and/or MRI evidence of further non-ADEM attacks and/or accrual of clinically-silent MRI lesions (which is not a component of ADEM).

Several studies have confirmed that the 2010 McDonald criteria perform better or similar to previous proposed pediatric MS criteria in children with non-ADEM presentations and in pediatric patients older than 11 years.[50-55] While a study from 52 patients has suggested inclusion of spinal cord imaging at first attack does not increase the accuracy of the 2010 McDonald criteria,[54] a retrospective investigation of 85 patients showed that the addition of spinal cord MRI was helpful in reaching DIS and DIT in 10% of the cases.[51]

MRI criteria in non-Caucasian populations

The 2010 McDonald criteria have been developed and mostly tested in typical adult Caucasian European and North American populations and their current formulation states that they require validation in Asian and Latin American populations.[10] Between 2011 and 2015, the performance of MRI diagnostic criteria has been tested in Korean,[56] Taiwanese,[57] Argentinean (including a sub-analysis applied only to non-European descendants, i.e., mestizos, natives and zambos),[58] and Russian[59] CIS patients, after careful exclusion of alternative neurological conditions, such as NMO/NMOSD in Korean patients.[56] All these studies provided evidence that the 2010 McDonald criteria apply well irrespective of world region.

Radiologically isolated syndromes (RIS)

The availability of MRI evaluation for indications unrelated to MS has led to an increased recognition of individuals with incidental brain lesions consistent with MS. Criteria have been proposed to identify imaging features that may be suggestive of a clinically asymptomatic demyelinating condition, including the fulfillment of at least three of four Barkhof criteria for DIS.[60, 61] The 2010 McDonald criteria concluded that "a firm diagnosis of MS based on incidental findings on MRI alone, even with additional supportive findings on evoked potentials or typical CSF findings in the absence of MS-relevant clinical symptoms, is problematic." A conservative approach was proposed, stating that persons cannot be diagnosed with MS based on MRI alone, and that at least one clinical event consistent with acute demyelination remains a cornerstone for MS diagnosis.

The use of advanced MRI techniques to characterize CNS involvement in RIS subjects has shown extensive axonal damage (measured using MR spectroscopy)[62] and a quite high percentage (40%) of subjects with CLs (which were more frequent in subjects with CSF OB, cervical cord lesions, and DIT on brain MRI).[63]

Approximately two-thirds of RIS subjects develop new lesions on longitudinal MRI scans and one-third of people with RIS develop neurological symptoms within five years, especially those with gadolinium-enhancing or spinal cord lesions.[64] In persons with clinically silent brain lesions consistent with MS, the presence of OBs, younger age, male sex, and abnormal visual evoked potentials identify individuals more likely to experience a sentinel clinical attack. Just focusing on MRI, the presence of gadolinium-enhancing lesions[65] and of asymptomatic spinal cord lesions (cervical or thoracic) are predictors of clinical evolution.[64, 66]

At present, there is the need for a more specific characterization of people with RIS and of prospective long-term studies to estimate the risk for these subjects to become MS. As a consequence, a firm recommendation concerning RIS is not possible. It is clear, however, even at this stage, that individuals bearing several risk factors need to be distinguished from those without these factors, since they are likely to have a prodromal condition, and that specific requirements are needed for a prompt diagnosis when the first symptom of CNS involvement occurs.

MRI in differential diagnosis (including atypical demyelination and NMO)

The exclusion of alternative diagnoses that can mimic MS is imperative in applying the 2010 McDonald criteria.[10] From an imaging perspective, many inherited and acquired disorders may manifest with evidence of DIT, DIS, or both and these should be included in the differential diagnosis of MS-like lesions. A timely recognition of imaging "red flags" in the work-up of patients suspected of having MS should alert clinicians to reconsider the differential diagnosis more extensively and perform some additional analyses.[67] Several reviews have been published on imaging features of the main acquired and inherited conditions that can enter the differential diagnosis of MS.[67-69]

In the 2010 McDonald criteria, a specific focus was the differential diagnosis between MS and NMO and NMO spectrum disorders (NMOSD). Up to 70% of NMOSD patients at onset have brain MRI lesions. The brain, optic nerve and spinal cord MRI findings of NMOSD patients have

been recently reviewed,[70] and revised diagnostic criteria for NMOSD have been proposed.[71] The International Panel for NMO diagnosis proposed the use of the unifying term NMOSD, which was stratified further by aquaporin-4 immunoglobulin G antibody (AQP4-IgG) testing. According to this revision, for patients with a positive AQP4-IgG test, at least one core clinical characteristic is required for NMOSD diagnosis; these include clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral presentations. For AQP4-IgG negative patients or patients with unknown AQP4-IgG status, more stringent clinical criteria, with additional neuroimaging findings, are required. In particular, acute optic neuritis requires brain MRI showing (1) normal findings or only nonspecific WM lesions, or (2) optic nerve MRI with a T2-hyperintense or T1-weighted gadolinium-enhancing lesion extending over 1/2 the optic nerve length or involving the optic chiasm. Acute myelitis requires an associated intramedullary MRI lesion extending over 3 contiguous segments (longitudinally extensive transverse myelitis-LETM) or 3 contiguous segments of focal spinal cord atrophy in patients with a history compatible with acute myelitis. The area postrema syndrome requires associated dorsal medulla/area postrema lesions. Finally, an acute brainstem syndrome requires associated peri-ependymal brainstem lesions.

High field and ultra-high field scanners

High field scanners (3.0 Tesla). Compared to 1.5 Tesla, the use of high field strength scanners (3.0) allows detection of a significantly higher number of lesions in CIS patients,[72, 73] with improved recognition of lesions involving the cortex,[74] infratentorial and periventricular regions.[72] The comparison of MRI criteria performance at 1.5 *vs* 3.0 Tesla in 40 CIS patients showed that one additional patient was diagnosed with DIS at high-field, without improvement for DIT.[75]

Ultra-high field scanners (7.0 Tesla). Ultra-high field MRI allows detection of a significant higher number of lesions,[76] better definition of lesions located in the WM and GM, their morphology and their association with the vasculature[77-81] at a resolution closer to that of histo-

pathological assessment than what was previously shown by using 1.5[82] or 3.0[83] Tesla scanners. Whether the assessment of lesion number and distribution using ultra-high field MRI scanners assists in making an earlier diagnosis of MS in CIS patients has not yet been evaluated. Several studies have identified some interesting lesion characteristics, which can aid the differential diagnosis between MS and other neurological conditions. The better definition of the relationship between demyelinating lesions and the intraparenchymal venous system, obtained by using T2*-weighted magnitude and phase imaging confirms pathological studies demonstrating that many MS plaques form around the microvasculature.[77-81, 84, 85] The perivenular lesion location can help to distinguish WM lesions in MS patients from incidental (ischemic) WM lesions.[81, 85] This finding has been reinforced by investigation of blood-brain barrier abnormalities in MS at 7 Tesla, which showed that the majority of enhancing lesions are perivenular and that the smallest lesions have a concentric pattern of enhancement, suggesting that they grow outward from a central vein.[86, 87] The presence of a central small vein and a rim of hypointensity on 7 Tesla T2*-weighted magnitude or FLAIR*[81] could be a distinctive feature of MS WM lesions, which may assist in the differentiation from lesions of patients with NMOSD[88] or Susac syndrome.[89]

A limited number of studies has tracked the longitudinal evolution of the previous abnormalities (Figure 3). A longitudinal study of 29 patients with possible but unclear diagnosis has shown the presence of a central vein in most lesions to accurately identify MS patients.[76] Another study has shown that ring phase lesions remained unchanged over a 2.5 year period in five RRMS patients,[90] whereas such a ring can be transient in acute lesions.[86, 87]

Summary

The Panel presents a synthesis of the main revisions or clarifications to the MRI component of the 2010 McDonald criteria for MS we propose.

There is evidence of some promising measures, which deserve further investigations before being moved (or not) to diagnostic criteria in the future:

- Identification of the central vein. What remains to be done is the standardization of sequences capable of showing these features on 3.0 and 1.5 Tesla scanners and creation of standardized definitions for identification of central veins. At present, centralized veins were counted if they 1) could be visualized in at least 2 perpendicular planes, 2) appeared linear in at least one plane, and 3) were completely surrounded by hyperintense signal in at least one plane ==(Figure 4)==.[85] Whether central veins are indeed confirmatory for MS lesions requires further study with appropriate disease comparisons.

- Identification of the hypointense lesional rim (on T2*-weighted magnitude and/or phase imaging images). What remains to be done is the performance of longitudinal studies (at both 3.0 and 7 Tesla); the clinical implementation and standardization of MR sequences among different vendors (at 3.0 Tesla); the analysis of the value in predicting conversion to MS and disability progression in CIS patients; the study of different MS disease clinical phenotypes and other neurological conditions, that can mimic MS.

- Identification of cortical pathology. Higher field strength imaging will identify CLs more reliably than conventional MRI, but is not likely to be available in clinical practice. More advanced techniques for CL identification at 3.0 Tesla may prove valuable in MS diagnosis. The definition of standardized guidelines for CL classification is also pending.

Closing remarks

Reading of MRI scans should be done in the appropriate clinical context. The premise of these guidelines and criteria is that we assume a basic knowledge of what constitutes a lesion. The largest linear measurement for lesion definition should be $\geq$ 3 mm in at least one plane of acquisition. Therefore, lesion identification should be done by expert and trained personnel. Image quality must be of high standard. A conservative approach in identifying lesions should be adopted.

In the diagnostic work up of patients with a suspicious of MS, the use of post-contrast sequences provides important pieces of information for the differential diagnosis. However, the

Food and Drug Administration (FDA) has recently made a safety communication for the long term effects of repeated gadolinium-based contrast agents (GBCAs), following the description of deposits of GBCAs in the brains of some patients who undergo four or more contrast MRI scans, long after the last administration (http://www.fda.gov/downloads/Drugs/DrugSafety/UCM455390.pdf).

MRI remains a valuable tool in identification of children and adults with MS- both at the time of an incident attack and when applied serially to confirm the chronic nature of this disease. More advanced imaging techniques inform on regional CNS involvement with greater sensitivity, and may add to diagnostic specificity. Whether MRI features consistent with MS in the absence of clinical involvement can confirm MS diagnosis remains an area of controversy that requires further deliberation, particularly given evidence that some such individuals demonstrate focal and global loss of tissue integrity yet are not currently eligible for MS-directed therapies. As higher strength imaging and newer sequences better approximate pathology-level interrogation of the CNS, the fundamental question of what defines a disease like MS will need to be answered.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "Clinically Isolated Syndrome", "Multiple Sclerosis", "McDonald criteria", "Diagnosis", "Differential diagnosis", "Cortical Lesions", "White matter", "Lesions", "Cortical Lesions", "Brain", "Spinal Cord", "MRI", "Optic Nerve"; "Disease Dissemination in Spce"; "Disease Dissemination in Time"; "Radiologically Isolated Syndromes"; "Pediatric MS"; "T1-hypointense lesions"; "Symptomatic Lesions", "Primary Progressive Multiple Sclerosis"; "Non-Caucasian Populations"; "Neuromyelitis Optica"; "Neuromyelitis Optica Spectrum Disorders"; "High Field"; and "Utra-high field" from 1979 until July 2015. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Conflict of interest statement

Authors' contribution. MF and FB had the idea of organizing the meeting, chaired it, and framed the structure of this manuscript. AR, FB, JSG, LK, MAR, MT, NDS, NE and OC participated to the meeting, summarized different aspects for the discussion and took part to the discussion. JF, CG, JP and DRS participated to the meeting and the discussion. BB and XM were involved after the meeting for critical discussion and revision. The complete manuscript was commented, revised and approved also by all authors.

Table 1. Proposed 2015 MAGNIMS DIS criteria
DIS can be demonstrated by the involvement* of at least 2 out of 5 areas of the CNS as follows:
≥ 3 periventricular lesions
≥ 1 infratentorial lesion
≥ 1 spinal cord lesion
≥ 1 optic nerve lesion
≥ 1 lesion involving the cortex

*If a subject has a brainstem or spinal cord syndrome, or optic neuritis, the symptomatic lesion(s) are not excluded from the criteria and contribute to lesion count.

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Figure legends

Figure 1. Examples of lesion classification based on integrated analysis of double inversion recovery (DIR) and magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequences. Top row: a hyperintense lesion close to the cortex is visible on DIR sequence (white arrow). MPRAGE sequence shows the location in the white matter of such a lesion. Middle row: a hyperintense lesion close to the cortex is visible on DIR sequence (white arrow). MPRAGE sequence shows the location close to the cortex (juxtacortical) of such a lesion. Bottom row: a hyperintense lesion close to the cortex is visible on DIR sequence (white arrow). MPRAGE sequence shows the intracortical location of such a lesion.

Figure 2. Spinal cord lesions from Fred

Figure 3. 7 T longitudinal lesions from Daniel

Figure 4. Pre-contrast 3T FLAIR* images (axial, sagittal and coronal views) of a 33-year-old woman with MS. A conspicuous central vein is clearly visible in the majority of hyperintense lesions. The definition of "perivenular" lesion requires the visualization of the central vein in at least two perpendicular views (arrows in magnified boxes).