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Current Perspectives in the MRI Diagnosis of Multiple Sclerosis: The 2016 Revised MRI Criteria

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MRI scanning is the main widely used diagnostic method for multiple sclerosis (MS). This article discusses the current state of the question of the effectiveness of using brain and spinal cord MRI scans in the diagnosis of patients with suspected MS. Particular attention is paid to the McDonald MRI and MAGNIMS criteria as revised in 2010 and 2016 for both remitting MS and primary progressive MS. The data presented here allow radiologists and neurologists to optimize the use of MRI scans in clinical practice for the diagnosis of MS.

Keywords: magnetic resonance tomography, multiple sclerosis, MRI criteria, remitting multiple sclerosis, primary progressive multiple sclerosis.

Magnetic resonance imaging (MRI) of the brain and spinal cord is the main diagnostic method for confirming clinical diagnoses of multiple sclerosis (MS). Confirmation of diagnoses of MS require assessment of two main key characteristics: dissemination of the pathological process in space and time. These are the basis of the MRI criteria for MS, which were published at the end of the 1980s and are periodically revised to account for the acquisition of new knowledge and clinical trial results. One revision of the McDonald criteria was made in 2005. These criteria applied to 2010, when, the McDonald 2010 criteria were recommended, with the aim of making diagnosis simpler and quicker.

Use of the 2010 McDonald MRI Criteria. During the last 30 years, the neurology community has adopted different diagnostic criteria, periodically modified after acquisition of new clinical data [1–4]. The treatment of this disease is known to have the greatest efficacy when at the early stage, such that the early, rapid, and accurate diagnosis of MS is particularly important. The 2010 revision of the diagnostic criteria is based on detection of lesions in the central nervous system (CNS), demonstrating dissemination of the pathological process in space and time. In addition, diagnostic criteria require exclusions of other alternative diagnoses [5, 6]. Thus, from the formal point of view, the diagnosis of MS can be made only on the basis of the clinical manifestations, though MRI investigations are required for confirmation of these key characteristics and exclusion of other CNS pathology.

In 2010, the International MAGNIMS group (Magnetic Resonance Imaging in MS) presented a review of the McDonald criteria (Table 1). This version provides for more sensitive MRI criteria. However, the specificity of the method was somewhat below that of the earlier updates – 2001 and 2005 [3, 7]. In the 2010 McDonald MRI criteria, the accent was placed not on assessments of the dissemination of the pathological process in terms of the number of plaques, but on their typical locations, which simplified interpretation of MRI scans. There was also no obligatory time period between the clinical attack and the first MRI investigation, such that an earlier start of observations of patient was facilitated. In addition, the concomitant presence of contrast medium (CM)-accumulating and -nonaccumulating plaques was included as an indicator of dissemination of the pathological process over time in some patients who had undergone single MRI scan investigations at any time since appearance of disease symptoms.

Previously there was no evidence that the neuroimaging characteristics of patients with remitting MS (rMS)

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TABLE 1. McDonald MRI Criteria 2010

Type of MS	Dissemination in space	Dissemination in time
rMS	One or more plaques in two or the four typical locations (periventricular, juxtacortical, subtentorial, and spinal). All symptomatic plaques located in the brainstem and spinal cord are excluded.	One of the following criteria: New plaque(s) on T2 and/or Gd^+ on T1 images on subsequent MRI scans regardless of when the first scan was obtained. Simultaneous presence of asymptomatic Gd^+ plaques and Gd on T1 images at any time, including first scanning.
ppMS	Two of the following three criteria: Presence of one or more plaques in the brain on T2 scans in at least one of the three typical locations (periventricular, juxtacortical, subtentorial). Presence of two or more plaques in the spinal cord on T2 images. Presence of oligoclonal IgG antibodies and/or increased liquor IgG level.	Progression of disease over one year (determined retrospectively or prospectively).

were significantly different from those of patients with primary progressive MS (ppMS) [8]. The 2010 modified McDonald MRI criteria were the first to include separate diagnoses of ppMS and rMS (see Table 1) [3, 9]. According to these criteria, the dissemination of the pathological process in space in ppMS is determined by two of the following three criteria: presence of one or more plaques in the brain on T2 scans, in at least one of the three MS-typical locations (periventricular, juxtacortical, subtentorial); the presence of two or more plaques in the spinal cord on T2 scans; and positive investigations for oligoclonal IgG antibodies in the cerebrospinal fluid (CSF).

Despite the advantages, the 2010 McDonald MRI criteria have been subject to criticism. It has been suggested that they may threaten diagnostic specificity – leading to overdiagnosis of MS. This risk is particularly high when MRI scan findings are analyzed without reference to the clinical and laboratory information or are interpreted by radiologists and clinicians lacking adequate experience in assessing brain and spinal cord lesions. Diagnostic difficulties also come from the lack of "neurological" skill on the part of MRI specialists, who must, in compliance with the 2010 MRI criteria, discriminate between symptomatic and asymptomatic plaques. It should be noted that CSF analysis to confirm the diagnosis of rMS is not required by the 2010 McDonald criteria, though these data may undoubtedly be of benefit to some patients [10].

It should be recognized that the 2010 McDonald MRI criteria significantly improved the process of rMS diagnosis, though they have a series of limitations in ppMS [3]. In these cases, despite improvements in contemporary instruments, MRI scans of both the brain and the spinal cord fail to reveal any features or abnormalities [11]. Thus, the diagnosis of ppMS can be made significantly more difficult.

We have discussed above that the 2010 revision of the McDonald criteria was partially based on the work of the MAGNIMS group, which studies patients of the europeoid race [9, 12]. There is a view that they may be applicable to the diagnosis of MS in people of Asiatic and Latin American origin, and patients of childhood age [3]. Data have been published on the specificity of the McDonald criteria in patients of this age group. One of these studies conducted a retrospective comparison of the 2005 and 2010 McDonald MRI criteria in a group of children in the phase of acute demyelination, followed by prospective follow-up for the next 24 months [13]. The researchers pointed out the high sensitivity and specificity of the 2010 McDonald criteria in children aged more than 11 years with clinical symptoms not linked with acute disseminated encephalomyelitis (ADEM). The results and conclusions of another multicenter retrospective study [14] also confirmed the high diagnostic value of the 2010 McDonald criteria in children.

After the discovery of optic neuromyelitis (Devic's syndrome) and optic neuromyelitis-associated syndrome, the accuracy of the 2010 McDonald MRI criteria in patients with clinically isolated syndrome (CIS) became comparable in patients of europeoid and Asiatic races [15].

Use of 2016 MRI Criteria for MS. MRI criteria were included in the diagnostic algorithm for patients with CIS suspected to have MS in 2001, after which there were a number of reviews. Since the 2010 update, there have not only been new data on the use of MRI scans in assessments of the dissemination of the process in space and time, but also improvements in MRI instruments, with the wide introduction of high-field tomographs (1.5 and 3 T) and new impulse sequences into clinical practice. These observations provided grounds for further review of the MRI criteria for MS by the MAGNIMS group in 2016.

These changes are reflected in Table 2, which shows that the criteria for the dissemination of the pathological process in space were evaluated.

Given that the presence of a single periventricular plaque is insufficiently specific for a demyelinating inflammatory process and that plaques can be detected in healthy people and patients with other neurological diseases [16], changes in the number of periventricular plaques were made

TABLE 2. MAGNIMS MRI Criteria, 2016

Type of MS	Dissemination in space	Dissemination in time
rMS	Presence of plaques in two of the five typical locations: ≥3 plaques periventricularly ≥1 plaque in the optic nerve ≥1 plaque juxtacortically/cortically ≥1 plaque subtentorially ≥1 plaque in the spinal cord The presence or absence of symptomatology associated with plaques in the brainstem, spinal cord, and optic nerve is not relevant	One of the following criteria: New plaque(s) on T2 and/or Gd^+ on T1 images on subsequent MRI scans regardless of when the first scan was obtained Simultaneous presence of asymptomatic Gd^+ plaques and Gd on T1 images at any time, including first scanning
ppMS	Two of the following criteria: Presence of one or more plaques in the brain on T2 scans in at least one of the three typical locations (periventricular, juxtacortical, subtentorial) presence of one or more plaques in the spinal cord on T2 scans Presence of oligoclonal IgG antibodies and/or increased liquor IgG level.	Progression of disease over one year (determined retrospectively or prospectively).

Note. All changes from the 2010 criteria are underlined.

as compared with those in the 2001 and 2005 McDonald criteria [1, 2]. The importance of the number of plaques was confirmed in a number of studies with analysis of a large cohort of 652 patients with CIS, which showed that patients not meeting the criteria for dissemination of the pathological process in space for MS but having three periventricular plaques in combination with age and the presence of oligoclonal antibodies were at high risk of developing MS [17]. In another study [18], patients aged under 40 years with CIS with spinal cord involvement with three or more periventricular plaques and synthesis of intrathecal immunoglobulin were identified as developing MS with a precision of 78%. In a multicenter study of 468 patients with kids, the presence of three periventricular plaques had significant prognostic value for transformation into MS within three years of follow-up [19]. A study comparing patients with MS and primary and secondary CNS vasculitis found that the presence of three or more periventricular plaques was the only MRI criterion allowing MS to be distinguished from systemic lupus erythematosus or Sjögren's syndrome [20].

The literature also focuses attention on the need to include the optic nerve as an additional element of the CNS, typical for MS, which can be involved in the pathological process. Visualization of clinically asymptomatic optic nerve inflammation (plaques on this nerve detected on MRI scans or thinning of the nerve fiber layer of the retina) also confirms dissemination in space in patients without visual impairments at the ongoing point in time – i.e., there is also dissemination in time [8].

The results of histological studies have shown that there is extensive involvement of the gray matter in the pathological process in MS [21]. The following subtypes of cortical plaques are identified in accordance with the locations of plaques in the cerebral cortex: subpial, purely intracortical, and plaques located on the boundary of the cortex and the subcortical white matter. Visualization of cortical plaques is quite difficult, especially when standard MRI protocols are used. A number of specific impulse sequences were suggested with the aim of improving the sensitivity with which cortical plaques are visualized, these including DIR, PSIR, and MPRAGE [22]. Nonetheless, many cortical plaques remain unseen on MRI scans, even on tomograms obtained at magnetic induction of 1.5 and 3 T [23]. Thus, changes in the MRI criteria lay not in the identification of new, cortical locations, but in expanding the term "juxtacortical location," which now means "juxtacortical/cortical location." Assessment of cortical plaques may also help in the differential diagnosis of MS against other diseases resembling MS (for example, cortical plaques are never seen in migraine or optic neuromyelitis and are very rare in healthy patients [21, 22].

In the 2010 McDonald criteria, assessment of dissemination of the pathological process in space does not consider plaques located in the brainstem or spinal cord. The recent review of the MRI criteria for MS eliminated this drawback, and all plaques now carry equal diagnostic significance. The recommendation for demonstrating dissemination of the pathological process in space is to visualize the whole spinal cord (especially in patients not meeting the criteria for dissemination of the process on MRI brain scans).

The division of types of MS course into rMS and ppMS is strictly clinical. Nonetheless, attempts have been made to find additional biomarkers for further discrimination of these clinical forms. In 2012, data from studies of the sensitivity of the use of criteria for spinal cord involvement and analysis of CSF for oligoclonal antibodies were published [24]. As a result of this study, the criteria for dissemination of the pathological process in space for the spinal cord in the MRI criterion for MS in the 2016 update was changed from two or more plaques to one or more plaques (with no importance attached to whether or not these plaques were clinically significant), which significantly simplified this criterion and increased its sensitivity (see Table 2). None-

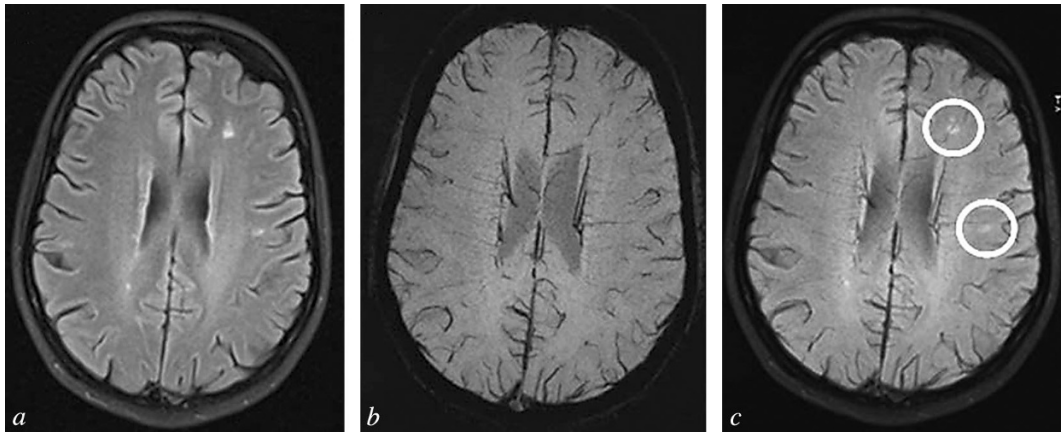

Fig. 1. Brain MRI scan from a patient with MS in FLAIR (*a*) and SWI (*b*) modes and the two combined (*c*). Scans show perivenular location of demyelination plaques in the FLAIR* image (venocentric pattern).

theless, further development of the criterion of the specificity of dissemination of the pathological process is needed.

The MRI criteria used to confirm dissemination of the process in space and time in MS can also be used in radiologically isolated syndrome (RIS) [25].

The current view is that the MRI criteria for MS can be used not only in people of the europeoid race, but also in patients from Asia and Latin America [14, 26]. However, unfortunately, there are as yet no reports addressing the use of the MRI criteria for MS in patients of African and Near-Eastern origin. In children aged over 11 years in whom ADEM has been excluded, the MRI criteria for a process disseminated in space and time can be applied as in adults, though in children under 11 years of age, even when ADEM has been excluded, more attention needs to be paid to application of the criteria [13].

Histological and MRI data have shown that diffuse (and irreversible) damage to the brain matter starts at the very earliest stages of MS. Timely detection of these changes can help identify patients at increased risk of developing severe disability. Standard MRI methods such as the T2 mode and the T1 mode after administration of contrast medium have high sensitivity for visualizing plaques in the white matter of the brain. Nonetheless, they lack sufficient specificity for identifying the nature of changes within plaques; they also lack the sensitivity required for detecting diffuse changes in the externally unaltered gray and white matter of the brain and spinal cord. Currently, the main task of investigators is to study and introduce state-of-the-art MRI methods developed to detect these changes.

One such state-of-the-art method is proton MR spectroscopy, which is performed in patients with CIS to identify the nature of changes in brain matter as well as plaques of demyelination visualized in the T2 mode. In patients with CIS, externally unaltered white matter (EUWM) showed a significant reduction in N-acetylaspartate (a marker for neuron damage) and an increase in myoinositol (a marker for glial cell damage). It is important to note that the magnitudes of these changes were greater in those patients who were subsequently given clinical diagnoses of MS [27]. Diffusion tensor MRI and magnetization transfer imaging have also identified differences in EUWM between CIS patients and controls. This provides grounds for suggesting that these methods may be of great value in prognosticating cognitive impairments and disability in these patients [28, 29].

Despite the fact that data from state-of-the-art MRI methods can provide information for assessment of the risk of developing MS, their sensitivity and specificity for the diagnosis and differential diagnosis in individual patients remain to be studied. These methods can be used to differentiate MS from other demyelinating diseases. Thus, ADEM, Devic's optic neuromyelitis, and Leber's optic neuropathy have been demonstrated to show more diffuse changes in brain matter than seen in typical MS [30, 31]. Nonetheless, there is a need for prospective studies to address the advantages of new MRI methods over standard MRI in the diagnosis and prognosis of MS for rapid treatment decisions.

Plaques accumulating contrast medium are new lesions, active at the time of study, while plaques not taking up contrast but visualized on T2 scans are older plaques of demyelination. Thus, the criteria for dissemination of the pathological process in time must be fulfilled when plaques are identified with the blood-brain barrier in different states regardless of whether they are associated with ongoing clinical symptomatology or not [32].

"Back holes" – hypointense plaques not accumulating contrast medium in the T1 regime – are areas in the brain matter with marked demyelination and axon death and are seen mostly in patients with a long history of illness and progressive types of disease. These changes in the T1 mode must also be considered in the MRI criteria. Thus, the presence of "black holes" on MRI scans in patients with CIS

may point to a not entirely favorable course of illness. However, it should be noted that these do not have prognostic value in relation to the transformation of CIS into MS [33]. The presence of chronic "black holes" is noted used as a potential alternative criterion for dissemination in time in adults, though it is best justified in children in differentiating MS from monophasic disease (such as ADEM).

Recognizing the undoubted value of MRI methods in the diagnosis of MS, further attention should be paid by physicians to the fact that some MRI changes are not specific for this disease. Thus, it should be noted that recent revisions of the McDonald MRI criteria are less strict and this, unfortunately, can sometimes lead to overdiagnosis of MS. Questions of differential diagnosis are therefore currently very relevant in relation to the use of MRI.

Potential targets for differential diagnosis include the periventricular location of plaques of demyelination and the suggested increase in iron deposition within them [34]. These signs are particularly clear in MRI with high magnetic induction ≥3 T) [35]. SWI (susceptibility-weighted imaging) pulse sequences, first described in 2004 [36], display high sensitivity in detecting small veins and areas containing iron, which has paramagnetic properties, in the brain. The use of SWI has additional potential for differential diagnosis, especially when SWI is performed and evaluated along with FLAIR results (which is termed FLAIR*) (see Fig. 1) [37].

Recent experience in the use of SWI in MRI scans with magnetic induction of 3–7 T has shown that most chronic and some acute plaques of demyelination in MS may have zones with decreased MR signal intensity. These hypointense changes are probably due to free radicals or iron deposits, though loss of myelin may also make a contribution to changes in the intensity of the MR signal on SWI images [38].

A significant proportion (>40%) of MS plaques have a small vein in the central area [39]. In a recent study using the 3D T1 regime, administration of contrast medium was followed by detection of a venocentric pattern on high-induction (3 T) MR tomographs in a majority of MS plaques (95%) [40]. The venocentric positioning of plaques and the presence of hypointense areas within them are specific markers and must be used in the differential diagnosis of patients with CIS or MS with other neurological diseases [41]. Thus, further studies need to be directed to studying these properties of SWI with the aim of increasing the specificity of MRI in the diagnosis of MS.

A further direction in the differential diagnosis of MS is detection of changes in cortical locations directly associated with cognitive impairments. Cortical plaques are found in significant numbers in patients with MS and are easily visualized using "double inversion recovery" (DIR) spike sequences, in which the intensity of the MR signal from the white matter and CSF is suppressed [34]. Thus, DIR improves the sensitivity of MRI for detecting cortical plaques in vivo [42], but remains unable to discriminate between types of cortical plaques [22]. More sensitive regimes for this are PSIR (phase-sensitive inversion recovery) and MPRAGE (high-resolution 3D magnetization-prepared rapid acquisition with gradient echo), which are run on instruments with high magnetic induction. Thus, simultaneous use of these sequences reveals at least one cortical plaque in 36% of patients with CIS, which is consistent with a high risk of transformation into clinically verified MS [43].

Repeat brain MRI scans are needed in patients with clinical and radiological data suggestive of MS but not yet completely fulfilling the MRI criteria for MS. The time interval between the first and next MRI scans is currently subject to discussion, though the optimum interval should be 3–6 months. This suggestion is based on the fact that most (80%) patients with CIS have at least three plaques in the white matter on first MRI scans, with the appearance of new plaques on subsequent T2 images [44]. If there are no new plaques in the white matter on the next MRI scan, the third scan can be performed at 6–12 months. These time intervals can also be used in patients with RIS. New active plaques appearing in patients with RIS on subsequent MRI scans significantly increase the risk that these patients will develop MS [45], though exact diagnoses of MS cannot be made without the appropriate clinical symptomatology.

The main aim of repeat brain MRI studies is to detect active plaques (i.e., new or expanding plaques in the T2 mode with or without take-up of contrast medium in the T1 mode). It is important for repeat MRI scans to be performed on the same instrument and using the same standardized MRI protocol as the first scan [46]. Adequate repositioning is also required for accurate evaluation of the sequences of MRI images being compared; conversely, incorrect repositioning can lead to artifacts which can imitate the changes seen in MS.

Thus, important elements in the MRI diagnosis supporting the clinical diagnosis of MS are: MRI scans should be performed by experienced specialists using a standardized MRI protocol including administration of contrast medium for detection of active plaques and making differential diagnoses against other diseases, and scan results should be interpreted by a medical radiologist with sufficient experience in analyzing images of this type. Even in multifocal brain lesions with MS-typical MRI changes, there is an undoubted need to compare MRI data with the neurological symptomatology and exclude other alternative diseases.

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