Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines
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MRI has improved the diagnostic work-up of multiple sclerosis, but inappropriate image interpretation and application of MRI diagnostic criteria contribute to misdiagnosis. Some diseases, now recognized as conditions distinct from multiple sclerosis, may satisfy the MRI criteria for multiple sclerosis (e.g. neuromyelitis optica spectrum disorders, Susac syndrome), thus making the diagnosis of multiple sclerosis more challenging, especially if biomarker testing (such as serum anti-AQP4 antibodies) is not informative. Improvements in MRI technology contribute and promise to better define the typical features of multiple sclerosis lesions (e.g. juxtacortical and periventricular location, cortical involvement). Greater understanding of some key aspects of multiple sclerosis pathobiology has allowed the identification of characteristics more specific to multiple sclerosis (e.g. central vein sign, subpial demyelination and lesional rims), which are not included in the current multiple sclerosis diagnostic criteria. In this review, we provide the clinicians and researchers with a practical guide to enhance the proper recognition of multiple sclerosis lesions, including a thorough definition and illustration of typical MRI features, as well as a discussion of red flags suggestive of alternative diagnoses. We also discuss the possible place of emerging qualitative features of lesions which may become important in the near future.

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Introduction

Since their introduction in 2001 up to the recent 2017 revision, the McDonald diagnostic criteria for multiple sclerosis are based on the number, size and location of brain and spinal cord lesions believed to be typical of multiple sclerosis. Lesion assessment on conventional T2-weighted and post-contrast T1-weighted MRI sequences has allowed the definition of criteria that support the early diagnosis of multiple sclerosis in patients with clinical symptoms characteristic of multiple sclerosis (Thompson et al., 2018).

By virtue of the requirement of demonstrating dissemination in space and time, these diagnostic criteria are highly sensitive, and when met in the context of a typical demyelinating event (i.e. subacute optic neuritis, incomplete transverse myelitis, and brainstem syndromes), have a very high positive predictive power for distinguishing early relapsing-remitting myelitis, and brainstem syndromes), have a very high sensitive, and when met in the context of a typical demyelination in space and time, these diagnostic criteria are highly characteristic of multiple sclerosis (Thompson et al., 2018).

These considerations provided the impetus to hold a workshop in December 2018 in Milan, Italy, which involved international experts in multiple sclerosis and MRI (Supplementary material). The main goal was to formulate practical guidelines for the correct interpretation and classification of lesions in multiple sclerosis patients that would be helpful both to clinicians involved in multiple sclerosis care and for research studies, ultimately contributing to more accurate diagnosis.

Three main topics were addressed during the workshop: (i) re-examination and definition of features characteristic for individual multiple sclerosis lesions and for patterns of their distribution (‘green flags’) as defined in the 2017 revision of the McDonald criteria (Thompson et al., 2018); (ii) depiction of lesion patterns that satisfy current multiple sclerosis diagnostic criteria, but are not characteristic of multiple sclerosis. They may be associated with other diseases mimicking multiple sclerosis, an artefact or an incidental lesion related to a comorbidity and constitute ‘red flags’ for multiple sclerosis diagnosis. Examples include ischaemic lesions, peculiar patterns of contrast enhancement, or age-related ‘periventricular capping’ on T2-weighted images. They also encompass distinctive MRI features of recently recognized antibody-mediated diseases (e.g. neuromyelitis optica spectrum disorders and anti-MOG-IgG disease); and (iii) discussion of emerging features of lesions (e.g. central vein sign, subpial demyelination and lesion rims), which are likely, in the near future, to improve specificity of the diagnostic algorithm for multiple sclerosis.

General considerations when using MRI for the diagnosis of multiple sclerosis

There are general considerations when applying the MRI aspects of the 2017 revision of the McDonald criteria in the diagnostic work-up of patients with suspected multiple sclerosis:
The clinical syndrome should be typical of demyelination.

(ii) The criteria should be applied to adult patients (between 18 and 50 years); however, they also perform well in identifying paediatric patients with multiple sclerosis from those suffering from monophasic demyelination (Fadda et al., 2018), although special care is needed in patients under 11 years (Thompson et al., 2018). In paediatric cases, the presence of at least one black hole (a hypointense lesion on T1-weighted sequence) and at least one periventricular lesion at baseline contribute to distinguish children with multiple sclerosis from those with monophasic demyelination (Verhey et al., 2011; Fadda et al., 2018). For a comprehensive review of multiple sclerosis differential diagnosis in pediatric population, see Banwell et al. (2016).

(iii) In patients older than 50 years or with vascular risk factors, more stringent criteria should be considered [e.g. a higher number of periventricular lesions (abutting the lateral ventricles, see below for details)].

(iv) MRI studies should be of adequate quality, with few artefacts and performed on scanners with a minimum field strength of 1.5 T. Using 3D acquisitions or 2D with 3-mm thick slices and no gap between slices (see Rovira et al., 2015; Traboulsi et al., 2016 for MRI protocols proposed and Table 1 for sequence suggestions) will increase diagnostic yield.

(v) Key MRI sequences include T2-weighted and T1 pre- and post-gadolinium images of the brain and the spinal cord (Table 1).

(vi) Multiple sclerosis lesions can occur anywhere in the CNS, and thus MRI of the cervical, thoracic and lumbar spine should be considered in patients with symptoms referable to these locations, and for detecting subclinical lesions (particularly in the spinal cord). Indeed, spinal cord assessment can be helpful in establishing dissemination in space when brain MRI findings are not conclusive and might provide significant prognostic information.

(vii) Fat-suppressed MRIs of the optic nerves should be considered especially in atypical cases to rule out possible alternative diagnoses.

(viii) Lesions should be confirmed on multiple planes to avoid false positive findings due to artefacts and false negative results (Table 1). The acquisition of 3D sequences [e.g. T2-fluid-attenuated inversion recovery (T2-FLAIR)] can allow multi-planar reconstruction, whilst, especially for 2D acquisitions, a second imaging sequence on a different plane (e.g. sagittal) should be acquired.

(ix) Serial imaging can support the diagnosis of multiple sclerosis, given that multiple sclerosis is characterized by the accrual of lesions over time and in new areas of the CNS.

(x) Interpretation of the MRI scans should be performed by trained (neuro)radiologists or clinicians deeply familiar with the features of multiple sclerosis and disorders considered in the differential diagnosis.

(xi) T2 lesions can increase, decrease or stabilize in size over time; more rarely, small lesions completely disappear.

(xii) The pattern of gadolinium-enhancement in multiple sclerosis is variable but almost always transient (2–8 weeks, although typically <4 weeks).

(xiii) For the diagnosis of multiple sclerosis, there should be at least one typical multiple sclerosis lesion in at least two characteristic regions [periventricular (abutting the lateral ventricles, see below for details)], infratentorial (Bink et al., 2006; Gramsch et al., 2011; Fadda et al., 2018), subpial demyelination (7 T T2* or MP2RAGE PSIR and/or 3D T1-weighted MPRAGE; T2-FLAIR less optimal) (i) in patients older than 50 years or with vascular risk factors; (vii) in patients suffering from monophasic demyelination (Verhey et al., 2011; Fadda et al., 2018) and thus MRI of the cervical, thoracic and lumbar spine should be considered in patients with symptoms referable to these locations, and for detecting subclinical lesions (particularly in the spinal cord). Indeed, spinal cord assessment can be helpful in establishing dissemination in space when brain MRI findings are not conclusive and might provide significant prognostic information.

Table 1 Optimal imaging sequence suggested for each lesion type

| Lesion category | Core sequence(s) for primary identification | Alternative confirmatory sequence(s) |
|-----------------|--------------------------------------------|------------------------------------|
| Pernitential     | T2-FLAIR (preferably 3D)                   | T2-weighted, PD-weighted, 3D T1-weighted MPRAGE |
| Juxtacortical/Cortical | T2-FLAIR (preferably 3D) (Cortical: DIR) | 3D T1-weighted MPRAGE, T2, DIR, PSIR (Cortical: 3D T1-weighted MPRAGE, PSIR; T2-FLAIR less optimal) |
| Infratentorial   | T2-FLAIR (preferably 3D) (Bink et al., 2006; Gramsch et al., 2011; Moraal et al., 2008; Wang et al., 2018) | T2, PD, 3D T1-weighted MPRAGE |
| Spinal cord (cervical + thoracic) | ≥2 sagittal sequences including STIR, T2, PD, PSIR or 3D T1-weighted MPRAGE | Axial T2 (Weier et al., 2012) |
| Gadolinium-enhancing lesions | Mildly/moderately T1 SE or GE after a single dose gadolinium-based contrast agent with ≥5-min delay —avoid heavily 3D inversion-prepared T1-weighted MPRAGE —no MT pulse | Pre-contrast T1 (optional) |
| Additional multiple sclerosis lesions not currently included in formal diagnostic criteria | 2D STIR (coronal) | 2D FSE (coronal) |
| Optic nerve      | Post-contrast fat-suppressed T1 (axial and coronal) | 2D STIR (axial) |
| Future pathophysiology-based characteristics | 3D T2* (with segmented EPI) | Alternatives (good contrast but lower resolution): 3D DIR, 2D/3D FSE T2, 2D/3D fat suppressed T2-FLAIR |
| Central vein sign | T2-FLAIR* (T2-FLAIR + T1* with segmented EPI) | SWI |
| Subpial demyelination | 7 T T2* or MPRAGE | PSIR and/or 3D T1-weighted MPRAGE; T2-FLAIR less optimal; DIR |
| Smoldering/slowly expanding lesions | Phase of 7 T T2*-weighted GRE | Phase of 3 T 3D T2* or SWI |
|                      | Longitudinal T2 or T1 images |

DIR = double inversion recovery; EPI = echo-planar imaging; FSE = fast spin echo; GE = gradient echo; GRE = gradient recalled echo; MPRAGE = magnetization-prepared rapid gradient echo; MT = magnetization transfer; PD = proton density; PSIR = phase-sensitive inversion recovery; SE = spin echo; STIR = short-tau inversion recovery; SWI = susceptibility-weighted imaging; T2-FLAIR = T2-fluid-attenuated inversion recovery.
ventricles), juxtacortical/cortical, infratentorial, spinal cord] to support dissemination in space (Thompson et al., 2018).

(xiv) Brain white matter lesions are common in patients with comorbid vascular disease or migraine, as well as healthy adult subjects, and as non-specific small, rounded deep white matter lesions sparing the periventricular zone and U-fibres can also contribute to some of the lesion burden present on imaging. Currently, it is rarely possible to distinguish whether individual lesions are attributable to demyelination or to a comorbidity.

(xv) Especially for patients with a small number of lesions, individual lesion characteristics (size, ovoid shape, orientation perpendicular to ventricles, T₁ hypointensity, pattern of enhancement) are important in determining whether they are characteristic of multiple sclerosis; for patients with a large number of lesions, the distribution (periventricular predilection, combinations of brain and cord lesions, etc.) is more relevant.

Multiple sclerosis lesion: definition

A lesion in multiple sclerosis is defined as an area of focal hyperintensity on a T₂-weighted (T₂, T₂-FLAIR or similar) or a proton density (PD)-weighted sequence. Typical multiple sclerosis lesions are round to ovoid in shape and range from a few millimetres to more than one or two centimetres in diameter. Generally, they should be at least 3 mm in their long axis to satisfy diagnostic criteria, although the topography should also be taken into consideration, for instance, a lesion <3 mm located in the floor of the fourth ventricle should be considered abnormal, as lesions and flow-related artefacts rarely occur in this location. Lesions should be visible on at least two consecutive slices to exclude artefacts or small hyperintensities, although in acquisitions with higher slice thickness (e.g. ≥ 3 mm), smaller lesions may be visible on a single slice.

Multiple sclerosis lesions typically develop in both hemispheres, but their distribution is often mildly asymmetric in the early stages. While lesions can occur in any CNS region, relative to other disorders that cause white matter lesions, multiple sclerosis lesions tend to affect specific white matter regions, such as the periventricular and juxtacortical white matter, the corpus callosum, infratentorial areas (especially the pons and the cerebellum) and the spinal cord (preferentially the cervical segment). How involvement of these areas should be assessed to evaluate dissemination in space in patients with suspected multiple sclerosis will be discussed in the following sections.

Periventricular lesions

A periventricular lesion is defined as a T₂-hyperintense cerebral white matter lesion in direct contact with the lateral ventricles, without intervening white matter. Lesions abutting (touching) the ventricles and located in the corpus callosum are included in this definition (Fig. 1 and Table 2). An exception to this definition is a lesion that abuts the lateral ventricles but is located in the deep grey matter (e.g. caudate nucleus or thalamus) (Filippi et al., 2016, 2018; Thompson et al., 2018).

Periventricular multiple sclerosis lesions are typically distributed along the deep medullary veins (perivascular), thus having their main axis perpendicular to the lateral ventricles. They have an ovoid shape on the axial plane and are generally defined as ‘Dawson’s fingers’. T₂-FLAIR sequences (preferably 3D) have a high sensitivity to detect periventricular lesions and to distinguish lesions from enlarged perivascular spaces (Wardlaw et al., 2013). A second sequence [e.g. T₂-weighted, PD-weighted or T₁-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE)] may increase the confidence in confirming periventricular involvement and in distinguishing periventricular ‘capping’ at the frontal and occipital horns of the lateral ventricles that occurs with normal ageing (Neema et al., 2009).

Lesions located close to the lateral ventricles are found in several other neurological conditions, including migraine (Absinta et al., 2012; Liu et al., 2013), ischaemic small-vessel disease (Wardlaw et al., 2013), neuromyelitis optica spectrum disorders (Jurynczyk et al., 2017; Cacciaguerra et al., 2019) and anti-MOG-IgG disease (Jurynczyk et al., 2017). Generally, in these conditions, lesions do not abut the ventricles and are not oriented with the long axis perpendicular to ventricles or in the corpus callosum. A common mistake contributing to misdiagnosis is the misclassification of white matter lesions that are close to, but in fact separated from the ventricular surface by normal-appearing white matter, as periventricular (Solomon et al., 2016a, 2019). Lesions touching the third and fourth ventricles, and lesions in the midbrain touching the cerebral aqueduct should not be counted as periventricular.

Particular attention should be paid to lesion morphology. Multiple sclerosis lesions often have an ovoid/round shape, while linear plate-like hyperintensities parallel to the body of the lateral ventricles (‘periventricular banding’ or ‘halo’) should not be considered as indicative of multiple sclerosis. Similarly, long lesions that parallel and involve the long axis of the corpus callosum, rather than are oriented perpendicular to the ventricles, occur in neuromyelitis optica spectrum disorders; such lesions may ultimately evolve into pencil-thin peri-ependymal lesions (Kim et al., 2015; Wingerchuk et al., 2015; Cacciaguerra et al., 2019).

Red flags for periventricular lesions include the presence of lacunar infarcts or microbleeds, suggestive of ischaemic small-vessel disease (Wardlaw et al., 2013) or confluent and symmetric white matter abnormalities, indicative of genetic or metabolic leukodystrophies (Kohler et al., 2018; Lynch et al., 2019). Periventricular lesions with predominantly temporal pole involvement can suggest not only cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Chabriat et al., 2009), but also other more recently defined inherited conditions, including cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) and cathepsin A-related arteriopathy with
Table 2 Characteristic lesion features that are typical (green flags), atypical (red flags) or excluded from lesion count

| Lesion category          | Green flags suggestive of multiple sclerosis | Red flags suggestive of alternative diagnoses | Features that favour exclusion from consideration in diagnostic criteria |
|--------------------------|---------------------------------------------|-----------------------------------------------|------------------------------------------------------------------------|
| Lesion                   | Shape: ovoid/round. Size: at least 3 mm along the main axis. Distribution: asymmetric. | Infarcts or microbleeds (amyloid angiopathy, cerebrovascular disease). Distribution: symmetric (leukoaryctosis). | Shape: linear (perivascular space, enlarged Virchow-Robin space). Size: ≤3 mm along the main axis. |
| Core lesions included in current diagnostic criteria | | | |
| Periventricular          | Location: abutting the lateral ventricles without intervening white matter. | Periaqueductal lesions (NMOSD). Peripendymal lesions surrounding the lateral ventricle (NMOSD). Infarcts or microbleeds (amyloid angiopathy, cerebrovascular disease). Extensive symmetric white matter lesions (leukoaryctosis). Rounded lesions centrally located in the corpus callosum ('snowball'-like lesion) (Susac syndrome). | |
| Juxtacortical/cortical   | Location: touching or within the cortex. | Infarcts or microbleeds. | |
| Infratentorial           | Location: brainstem, cerebellar peduncles and cerebellar hemispheres; contiguous to cisterns or the floor of the fourth ventricle; surface of the pons and the pontine trigeminal root entry zone; lining of CSF border zones; cerebral peduncles and deep to the periaqueductal grey matter; unilater or bilateral peramedian location in medulla oblongata. | Infarcts or microbleeds (amyloid angiopathy, cerebrovascular disease). Symmetric lesions in the central pons (amyloid angiopathy, cerebrovascular disease). Periaqueductal lesions (NMOSD). Area postrema lesions (NMOSD). Medullary lesions contiguous to cord lesions (NMOSD). | |
| Spinal cord              | Multiple discrete (focal) lesions. Shape: sagittal: cigar-like; axial: wedge-shaped. Size: small; ≤ 2 vertebral segments; greater than half of the cord. Location: cervical > thoracic; peripheral region; lateral and posterior columns, but central grey matter not spared. Signal characteristics: T1 hypointensity (greater than at higher field strengths). | Longitudinal extensive transverse myelitis affecting ≥3 vertebral segments (NMOSD). Leptomeningeal/root enhancement (neuromyelitis optica). Cavities (syringohydromyelia). Micro/macrobleeds and ischaemic lesions (arteriovenous fistula, ischaemic myelopathy). Indistinct/diffuse/increasing (malignancy). Lesion involving only the grey matter (NMOSD, infections, ischaemic myelopathy). Large or multiple closed-ring enhancement (ADEM, malignancy, infarction). (Lepto)meningeal/root enhancement (neuromyelitis optica). Trident sign (neuromyelitis optica). Pancake sign (spinal corditis). Punctate or miliary enhancement (CLIPPERS, vasculitis, PML, Susac syndrome). Band-like enhancement (Baló's concentric sclerosis). Cloud-like enhancement (NMOSD). Purely cortical enhancement (vasculitis, ischaemic lesion). Persistence of enhancement >3 months (malignancy). | |
| Gadolininium-enhancing lesions | Shape: nodular; open-ring; closed-ring. Location: brain > spinal cord. | | |
| Additional features      | Size: small length. Location: unilateral optic nerve. | Size: long optic nerve lesion (NMOSD, anti-MOG-antibody mediated disease). Location: posterior optic nerve involvement also including the chiasm; simultaneous bilateral optic nerve involvement (NMOSD, anti-MOG-antibody mediated disease). | |

ADEM = acute disseminated encephalomyelitis; CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; PML = progressive multifocal leukoencephalopathy; NMOSD = neuromyelitis optica spectrum disorder.
strokes and leukoencephalopathy (CARASAL) (Lynch et al., 2019). Multifocal, rounded brain lesions, often centrally located in the corpus callosum (‘snowball’-like lesions) are suggestive of Susac syndrome (Kleffner et al., 2016), while ‘cloud-like’, poorly margined lesions in the corpus callosum, sometimes with a marbled pattern are described in neuromyelitis optica spectrum disorders (Fig. 1 and Table 2) (Kim et al., 2015; Wingerchuk et al., 2015).

Juxtacortical or cortical lesions

A juxtacortical lesion is defined as a T2-hyperintense white matter lesion abutting, i.e. in direct contact with, the cortex without intervening normal white matter. They are best detected using a T2-FLAIR sequence (preferably 3D) (Filippi et al., 1996; Moraal et al., 2008; Gramsch et al., 2015). In multiple sclerosis, juxtacortical lesions typically involve the U-fibres and can be located in all brain lobes and in the cerebellum (Fig. 2 and Table 2) (Pareto et al., 2015).

Lesions close to the cortex can occur with ageing and in other neurological diseases, including migraine (Absinta et al., 2012; Liu et al., 2013) and ischaemic small-vessel disease (Wardlaw et al., 2013). However, in these conditions, lesions are typically in the deep white matter with a rim of white matter separating them from the cortex. Importantly, U-fibres are generally spared by hypoxia and cerebrovascular diseases, since these fibres are well vascularized by both cortical branches and medullary arteries.

Cortical lesions are defined as focal abnormalities completely within the cortex or spanning the cortex and subjacent white matter. In multiple sclerosis, these lesions are...
usually well depicted using T2-FLAIR but may be better detected/localized with specialized MRI sequences, such as double inversion recovery (DIR), phase-sensitive inversion recovery (PSIR) or T1-weighted MPRAGE (Fig. 2) (Nelson et al., 2008; Geurts et al., 2011; Sethi et al., 2012).

Imaging of cortical lesions in multiple sclerosis is challenging due to technical issues and to their pathological features (i.e. most of them involve only the more superficial, less myelinated layers of the cortex). Thus, guidelines based on lesion signal characteristics and size have been proposed. Mandatory criteria for cortical lesion definition on DIR images are: (i) hyperintensity compared to adjacent normal-appearing grey matter; and (ii) size of at least 3 pixels (i.e. at least 3 mm along the main in-plane axis), based on at least 1.0 mm² in-plane resolution (Geurts et al., 2011). On PSIR and MPRAGE sequences, cortical lesions are hypointense relative to the surrounding normal cortex and they must involve the cortex, in part or whole. A lesion confined to the cortex is called intracortical. Different types of intracortical lesion have been described histopathologically (Bo et al., 2003). Type I lesions are cortico-subcortical lesions affecting both grey matter and white matter. Such lesions that involve both the cortex and juxtacortical white matter are called leukocortical (Sethi et al., 2012). Type II lesions are small perivenous intracortical lesions not affecting white matter or the pial surface. Type III lesions are characterized by demyelination extending inward from the pial surface of the brain (i.e. subpial demyelination) and are the most frequent type of cortical lesions. Finally, type IV are lesions extending through the whole cortical width but without passing its border with the white matter.

To improve cortical lesion detection, training is recommended to avoid the inclusion of artefacts, which are relatively common on DIR and PSIR sequences, and to exclude unusual signals from biological structures (e.g. cortical vessels). The identification of such lesions on consecutive slices and with several different MRI sequences is of particular importance for proper evaluation of cortical lesions.

Based on their morphology on MRI, cortical lesions have also been subclassified by shape as curvilinear/worm-shaped (lesions that follow the contour of sulcal and gyral folds), oval or wedge shaped (Calabrese et al., 2010; Sethi et al., 2013). Of note, curvilinear/worm-shaped lesions are only described in multiple sclerosis.

Current diagnostic criteria (Thompson et al., 2018) and guidelines (Filippi et al., 2016) for multiple sclerosis diagnosis acknowledge that clinical MRI scanners (e.g. 1.5 T and 3.0 T strength) cannot reliably distinguish between intracortical, leukocortical, and juxtacortical lesions. Moreover, advanced MRI sequences recommended for their identification are not widely applied in the clinical setting and can be difficult to interpret (Filippi et al., 2019). Therefore, for practical reasons, the definition of juxtacortical involvement has been expanded to include all three types of lesion (Filippi et al., 2016; Thompson et al., 2018).

Cortical lesions are a distinctive feature of multiple sclerosis and facilitate identification of patients with clinically isolated syndromes who are at higher risk of developing a second clinical attack (Filippi et al., 2010, 2018; Preziosa et al., 2018). Cortical lesions are not found in other conditions mimicking multiple sclerosis, such as migraine (Absinta et al., 2012). Although typically not described in neuromyelitis optica spectrum disorders (Calabrese et al., 2012; Cacciaguerra et al., 2019) they have been shown in a minority of patients (around 3%) with this condition (Kim et al., 2016), during the acute stage of the disease and tend to disappear during follow-up, resembling, in some cases, posterior reversible encephalopathy syndrome-like patterns. On the other hand, they do occur in other vascular disorders, such as vasculitis.

Red flags for juxtacortical involvement include: small cortical infarcts (diffusion restriction or spontaneous T1-hyperintensity suggestive of cortical laminar necrosis); multiple subcortical white matter lesions (ischaemic small-vessel disease); multiple well-defined CSF-like abnormalities with a dot or stripe appearance (enlarged Virchow-Robin spaces); hypointensity on T2-weighted images suggestive of lobar microbleeds; leptomeningeal/cortical hyperintensities on T1-weighted images associated with hypointensity on gradient-echo images (CNS vasculitis); and lesions with ill-defined borders in progressive multifocal leukoencephalopathy (Fig. 2 and Table 2).

**Infratentorial lesions**

An infratentorial lesion is defined as a T2-hyperintense lesion in the brainstem, cerebellar peduncles or cerebellum. These lesions commonly occur near the surface, or when more centrally usually have an ovoid/round shape, e.g. along the trigeminal tract. They may range from single, well-delineated lesions to discrete sub-pial ‘linings’ along the periphery of the brainstem (Fig. 3 and Table 2). In the pons, most lesions are contiguous with the cisterns or involve the floor of the fourth ventricle (often affecting the medial longitudinal fasciculus), the pontine surface and the pontine trigeminal root entry zone (intra-pontine trigeminal tract), regions rich in myelin and close to CSF (Fig. 3 and Table 2). Pontine lesions also frequently occur in ischaemic small-vessel disease. However, ischaemic changes associated with vascular diseases and hypoperfusion tend to involve the central pons along the transverse pontine fibres, which corresponds to a vascular border zone, supplied by different penetrating arteries arising from the basilar and superior cerebellar arteries (Wardlaw et al., 2013), while multiple sclerosis lesions are usually located at the periphery of the pons. Ischaemic abnormalities typically involve the central pontine white matter symmetrically.

In the midbrain, multiple sclerosis lesions are often located in the cerebral peduncles and close to the periaqueductal grey matter, while in the medulla oblongata, they typically have a uni- or bilateral paramedian location.
Figure 2 Characteristics of cortical/juxtacortical multiple sclerosis that are typical (‘green flags’) and atypical (‘red flags’), as well as those that should not be included. Top left: Green flags: examples of (A) juxtacortical lesions and (B) cortical lesions suggestive of multiple sclerosis. Top right: (C) white matter lesions not touching the cortex or within the cortex (subcortical). Bottom: Red flags: (D) multiple white matter lesions involving subcortical and deep white matter, suggestive of small-vessel disease; (E) lesions involving the grey matter-white matter border of different brain lobes with ill-defined borders in progressive multifocal leukoencephalopathy; (F) multiple well-defined CSF-like abnormalities that appear as dots or stripes in enlarged Virchow-Robin space; (G) hypointensity on T2-weighted sequence suggesting haemosiderin deposit due to a microbleed; (H) multiple leptomeningeal/cortical hyperintensities on T1-weighted imaging with associated hypointensity on gradient-echo sequence in CNS vasculitis. JC/CL = juxtacortical/cortical.
Multiple sclerosis lesions can occur in any portion of the cerebellar white matter and peduncles, frequently involving the middle and superior cerebellar peduncles (Fig. 3). However, prominent involvement of this region is also seen in anti-MOG-IgG disease and progressive multifocal leukoencephalopathy.

Two of the most specific brain MRI abnormalities of patients with neuromyelitis optica spectrum disorders typically locate to infratentorial regions (Kim et al., 2015; Wingerchuk et al., 2015; Cacciaguerra et al., 2019). Lesions in neuromyelitis optica spectrum disorders may occur around the cerebral aqueduct (periaqueductal) and in the dorsal brainstem adjacent to the fourth ventricle including the area postrema and the solitary tract (tractus solitarius); such lesions may lead to aqueductal stenosis and obstructive hydrocephalus (Clardy et al., 2014). When lesions occur in the area postrema, often as paired discrete lesions, they are frequently associated with the so-called ‘area postrema syndrome’ of intractable vomiting and hiccoughs, which is a well-recognized presentation of neuromyelitis optica spectrum disorders. Medullary lesions, including those associated with area postrema syndrome, may be contiguous with cervical cord lesions.

Red flags for infratentorial involvement include fluffy, cloud-like lesions involving the brainstem, in particular areas adjacent to the fourth ventricle and the cerebellar peduncles, which can occur with anti-MOG-IgG disease (Jarius et al., 2016a; Jurynczyk et al., 2017). Neuro-Behçet (Al-Araji and Kidd, 2009) is associated with typically large diencephalic and infratentorial lesions. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) lesions dominate in the brainstem and cerebellum, although they may also occur in the supratentorial white matter, diencephalon, basal ganglia and spinal cord; typically lesions have a miliary pattern with curvilinear enhancement of individual lesions (De Graaff et al., 2013; Blaabjerg et al., 2016; Tobin et al., 2017).

**Spinal cord lesions**

Multiple sclerosis spinal cord lesions are often multiple and short in cranio-caudal diameter. They are hyperintense on T2-weighted sequences and may occur along the entire spinal cord (cervical, thoracic or lumbar), although the cervical portion is more frequently involved (Lycklama et al., 2003; Bot et al., 2004; Weier et al., 2012; Gass et al., 2015; Ciccarelli et al., 2019). To be confident that they are not artefacts, lesions should be identifiable on at least...
two sequences [T₂ plus short tau inversion recovery (STIR) or PD images] or in two planes (Ciccarelli et al., 2019).

Historically, two different types of spinal cord lesion have been described in patients with multiple sclerosis: discrete (focal) and those where diffuse abnormal areas of intermediate signal intensity lack a well-demarcated border (Lycklama et al., 2003). These signs are not incorporated into current multiple sclerosis diagnostic criteria (Thompson et al., 2018) because they are not sufficiently reliable and specific (Polman et al., 2005). Therefore, to be considered as supporting a diagnosis of multiple sclerosis, spinal cord lesions should be focal, with clearly demarcated borders (Lycklama et al., 2003, 2019), cigar-shaped on sagittal images, and wedge-shaped on axial images (Fig. 4 and Table 2).

Multiple sclerosis lesions are often small (but at least 3 mm), covering less than two vertebral segments and usually less than half of the cord area (Lycklama et al., 2003; Bot et al., 2004; Weier et al., 2012; Gass et al., 2015; Ciccarelli et al., 2019). On axial images, most lesions are located in the periphery of the spinal cord, mainly in the lateral or dorsal columns, but they can affect the anterior white matter and the central grey matter (Lycklama et al., 2003; Weier et al., 2012; Gass et al., 2015; Kearney et al., 2016; Ciccarelli et al., 2019). Focal lesions strictly confined to the grey matter are unusual in multiple sclerosis. Although previously described as rarely hypointense on T₁-weighted images (unlike neuromyelitis optica spectrum disorder lesions, which are typically T₁ hypointense) (Ciccarelli et al., 2019), it is now established that multiple sclerosis cord lesions are frequently T₁ hypointense when imaged with higher field strengths (especially on 3D inversion-prepared gradient-echo sequences) (Nair et al., 2013; Valsasina et al., 2018) or when PSIR sequences are acquired (Kearney et al., 2015).

Active multiple sclerosis spinal cord lesions enhance less frequently than brain lesions (Kidd et al., 1996; Thorpe et al., 1996). When enhancement is present, it is typically short-lived (2–8 weeks, although typically <4 weeks) and nodular, while ring-enhancement (usually open) is less common (Pyle et al., 2009; Klawiter et al., 2010). Focal

Figure 4 Characteristics of spinal cord multiple sclerosis lesions that are typical (‘green flags’) and atypical (‘red flags’), and those that should not be included. Top left: Green flags: examples of (A) spinal cord lesions in the cervical and thoracic cord on sagittal short-tau inversion recovery sequence; (B) cervical cord lesions showing hypointensity on T₁-weighted sequences at 3 T (green arrowheads); (C) a cervical cord lesion showing involvement of the lateral column and central grey matter (green arrows) on T₂-weighted and phase sensitive inversion recovery sequences. Top right: (D) ‘Diffuse’ spinal cord lesions with ill-defined borders not included for the definition of spinal cord involvement. Bottom: Red flags: (E) longitudinally extensive transverse myelitis affecting more than three vertebral segments in neuromyelitis optica spectrum disorder; (F) longitudinally extensive spinal cord lesion affecting more than three vertebral segments associated with leptomeningeal and peripheral spinal cord contrast-enhancement in neuro-sarcoidosis; (G) extensive and selective involvement of lateral and posterior columns in subacute combined neurodegeneration; (H) spinal cord cavities in syringomyelia; (I) extensive T₂-hyperintense lesion extending rostrally from the conus, with spotted and tortuous regions of contrast enhancement in an arteriovenous fistula; (J) hyperintense lesion in the anterior portion of the thoracic spinal cord extending for more than two vertebral segments in a case of subacute ischaemic myelopathy; (K) T₂-hyperintense lesion of the cervical cord showing ‘pancake-like’ gadolinium enhancement in a case of spondylotic myelopathy. SC = spinal cord.
spinal cord swelling is frequently observed in the acute phase.

Spinal cord lesions are not seen with normal ageing or in the majority of common neurological disorders, such as migraine and cerebrovascular diseases (Lycklama et al., 2003). Spinal cord lesions can occur in some conditions like spondylotic myelopathy (Flanagan et al., 2014) or when dural fistulas or arteriovenous malformations are present (Condette-Auliac et al., 2014). Finding multiple short-segment spinal cord lesions is highly specific for multiple sclerosis and only rarely occurs in other inflammatory CNS diseases (neuromyelitis optica spectrum disorders, anti-MOG-IgG disease, acute disseminated encephalomyelitis, CLIPPERS and primary vasculitis of the CNS), infections (e.g. syphilis), neoplasms, toxic, metabolic and hereditary disorders (Geraldes et al., 2018; Ciccarelli et al., 2019).

Red flags for spinal cord lesions include longitudinally lesions extending over three or more vertebral segments, prominent involvement of the central grey matter, swelling of the spinal cord (neuromyelitis optica spectrum disorders, anti-MOG-IgG disease), preferential involvement of the most caudal portion of the spine (anti-MOG-IgG disease) (Dubey et al., 2018), leptomeningeal or nerve root involvement (neurosarcoidosis, infectious disease, malignancies), cavitation (syringohydromyelia), the presence of long and selective involvement of white matter columns (metabolic diseases such as vitamin B12 or copper deficiency), evidence of micro/macrobeeds (arteriovenous fistula), lesions affecting the anterior two-thirds of the spinal cord with the so-called ‘snake eye’ or ‘owl’s eye’ sign of bilateral hyperintensities of the anterior grey matter horns (ischaemia or infarction) or the presence of spinal cord compression as occurring in spondylotic myelopathy (Fig. 4 and Table 2) (Geraldes et al., 2018; Ciccarelli et al., 2019).

Gadolinium-enhancing lesions

Gadolinium enhancement plays an important role in the evaluation of patients suspected of multiple sclerosis. Safety concerns regarding gadolinium administration and its tendency to accumulate in the brain can be mitigated by the use of macrocyclic rather than linear agents and by controlling the frequency of administration at follow-up (Guo et al., 2018). It can support dissemination in time when it occurs in some lesions but not others at the time of initial presentation with a demyelinating syndrome (Thompson et al., 2018). Enhancement in new inflammatory demyelinating lesions is a short-lived feature (typically 2–8 weeks, although typically <4 weeks) in most cases, thus generally differentiating recent from older lesions (Rovira and Barkhof, 2018). Lesions that enhance for longer than 3 months are exceptional and should raise the possibility of alternative pathology, including sarcoidosis or vascular abnormality such as developmental venous anomaly or capillary telangiectasia (which can be confirmed using susceptibility-weighted imaging) (El-Koussy et al., 2012).

An enhancing lesion is defined as an area of at least 3 mm with a clear area of hyperintensity on T1-weighted images obtained at least 5 min after contrast agent administration (Fig. 5 and Table 2). They are best appreciated on moderately T1-weighted spin-echo or gradient-echo images but are more difficult to detect on heavily T1-weighted images (such as MPRAGE or PSIR) due to the higher background white matter signal. Although definitive assessment of signal enhancement requires pre-contrast images, spontaneous T1-hyperintensity (e.g. with calcification, haemorrhage, melanin) is very rare in multiple sclerosis lesions. However, as this might be observed in the presence of lipid- and iron-laden microglia/macrophages (Cakirer et al., 2003), a pre-contrast T1 weighted sequence can help to discriminate this cause of T1 hyperintensity from true contrast-enhancement. Gadolinium enhancement should be confirmed by a corresponding abnormality on T2 or T2-FLAIR images, and if absent, more likely represents flow artefact from nearby vessels or a capillary telangiectasia.

Enhancing multiple sclerosis lesions are often nodular, though larger ones can evolve into ring-enhancing lesions. Larger lesions, particularly those that abut the ventricles or the cortex, can show ‘open-ring’ enhancement (open towards the side that abuts ventricles or grey matter), which assists with differentiation from neoplastic lesions or abscesses; however, some large multiple sclerosis lesions may have closed-ring enhancement. Leptomeningeal enhancement is extremely rare in multiple sclerosis on post-contrast T1-weighted sequence, and if extensive should raise the suspicion of alternative pathology such as (neuro)sarcoid and granulomatous diseases, especially if located at the base of the brain. However, application of post-contrast T2-FLAIR sequence allows the presence of focal leptomeningeal enhancement in multiple sclerosis patients to be detected, especially in those with the progressive forms of the disease (Absinta et al., 2015). Other red flags include punctate or miliary enhancement (seen in CLIPPERS, vasculitis, progressive multifocal leukoencephalopathy, Susac syndrome), band-like enhancement (Baló’s concentric sclerosis), cloud-like enhancement (neuromyelitis optica spectrum disorders), purely cortical enhancement (subacute ischaemia) or patchy and persistent (capillary telangiectasia) (Charil et al., 2006; Miller et al., 2008; Geraldes et al., 2018). In the cord, specific red flags (Ciccarelli et al., 2019) include subpial enhancement and the ‘trident sign’ (subpial enhancement combined with enhancement of the central spinal canal) on axial images in (neuro)sarcoidosis and, more rarely in vitamin B12 deficiency (Paliwal et al., 2009), the ‘pancake’ sign in cervical spondylosis with cord compression and patchy/punctate or large ring enhancement in neuromyelitis optica spectrum disorders.
Optic nerve lesions

Although optic nerve imaging is not required in the current multiple sclerosis diagnostic criteria to demonstrate dissemination in space, it can be helpful in confirming optic nerve involvement in multiple sclerosis and can exclude alternative diagnoses for atypical optic neuropathies (Glisson and Galetta, 2009; Toosy et al., 2014; Filippi et al., 2016; Traboulsee et al., 2016).

Optic nerve imaging for lesion identification should include coronal fat-suppressed T2-weighted sequences with submillimetre in-plane resolution (ideally 0.5 mm × 0.5 mm or better) and slice thickness of ≤3 mm. 2D coronal STIR and 2D coronal fast spin-echo with fat suppression are typically used (Gass et al., 1996; Onofrj et al., 1996; Glisson and Galetta, 2009). Alternatively, 3D DIR (Hodel et al., 2014) and 2D/3D fat-suppressed T2-FLAIR (Aiken et al., 2011; Boegel et al., 2017) offer good contrast, fat and fluid suppression, but slightly lower spatial resolution (Toosy et al., 2014; Traboulsee et al., 2016).

For the detection of acute lesions, a post-contrast fat-suppressed T1-weighted spin-echo or gradient-echo sequence is recommended. A pre-contrast non-fat-suppressed T1-weighted sequence is usually acquired, which can help to rule out possible alternative diagnoses such as intracranial masses or extraocular muscle abnormalities. Slices should be ≤3-mm thick and should cover the whole length of the optic nerve from globe to the optic chiasm.

Typical acute optic nerve lesions are characterized by T2 hyperintensity, associated optic nerve swelling and contrast-enhancement. However, these findings are not multiple sclerosis-specific, since they can occur in other inflammatory conditions, including neuromyelitis optica spectrum disorders (Kim et al., 2015), ischaemic or infectious diseases. Post-acute or chronic lesions exhibit atrophy and T2 hyperintensity. Red flags for the optic nerve include: posterior optic...
nerve involvement also including the chiasm, suggestive of anti-AQP4-IgG-seropositive neuromyelitis optica spectrum disorders, simultaneous bilateral optic nerve involvement and a long optic nerve lesion, suggestive of neuromyelitis optica spectrum disorders and especially anti-MOG-IgG disease (Kim et al., 2015; Akaishi et al., 2016; Ramanathan et al., 2016). A T2-hyperintense lesion in the nerve can differentiate multiple sclerosis from ischaemic and toxic optic neuropathies or Leber’s hereditary optic neuropathy that do not show acute T2-hyperintense lesions in the optic nerve.

Perioptic nerve sheath enhancement is a recognized phenomenon in optic neuritis although soft tissue enhancement extrinsic to the nerve, affecting the orbit, orbital apex or cavernous sinus signifies a non-multiple sclerosis aetiology [e.g. granulomatous disease, tumour, infection, anti-MOG-IgG disease (Jarius et al., 2016)].

Areas of ongoing research

Central vein sign

Multiple sclerosis lesions typically form around veins and venules, and the relation between focal lesions and venules can be best visualized (through the central vein sign) at ultra-high field strength (7.0 T), but is also seen at 3.0 T and 1.5 T (Sati et al., 2016; Maggi et al., 2018). Cerebral veins can be imaged using high resolution 3D T2*-weighted gradient-echo MRI (preferably with segmented echo-planar imaging), which can be fused with T2-FLAIR to form T2-FLAIR* images. Conventional susceptibility-weighted images, while sometimes demonstrating central veins, are generally inferior (Sati et al., 2016). Gadolinium administration, during or shortly before acquisition, can improve central vein sign detection at lower field strength (1.5 T), but is not required at 3.0 T or higher (Sati et al., 2016).

Recommendations for use in clinical practice define central vein sign as a thin hypointense line or small dot (<2 mm) that is visible in at least two planes and appears as a thin line in at least one plane. The vein should run partially or entirely but centrally through the lesion (Sati et al., 2016). Lesions <3 mm, confluent lesions, and lesions where multiple veins are seen or the vein is not clearly defined should be excluded (Sati et al., 2016). On average, the central vein sign can be detected in ~80% of lesions in all stages of multiple sclerosis, although less frequently in intracortical lesions (Kilsdonk et al., 2014). Identifying the central vein sign is more difficult in infratentorial and spinal cord lesions. The vein sign is more difficult in infratentorial and spinal cord lesions.

Recent studies show that the proportion of lesions with a central vein sign is higher in multiple sclerosis (Sati et al., 2016) than in other conditions, including neuromyelitis optica spectrum disorders (Sinnecker et al., 2012; Kister et al., 2013; Cortese et al., 2018), CNS inflammatory vasculopathies (Maggi et al., 2018), migraine (Solomon et al., 2016b), Susac syndrome (Wuerfel et al., 2012), cerebrovascular diseases (Kilsdonk et al., 2014; Mistry et al., 2016; Campion et al., 2017; Samaraweer et al., 2017), and incidental cerebral white matter lesions (Tallantyre et al., 2011). Different criteria have been proposed for multiple sclerosis diagnostic work-up, including a minimum percentage of lesions showing central vein sign for multiple sclerosis diagnosis (Mistry et al., 2013, 2016; Campion et al., 2017; Cortese et al., 2018), and a simplification based on the presence of three (Solomon et al., 2018) or six (Mistry et al., 2013) characteristic lesions. Automated methods of detecting the central vein sign are emerging (Dworkin et al., 2018). Large, prospective multicentre trials including patients at first presentation of neurological signs are still needed to evaluate the clinical value of the central vein sign for multiple sclerosis diagnosis.

Subpial demyelination

In multiple sclerosis, subpial demyelination is sometimes associated with meningeal inflammation, and intrathecal pro-inflammatory profile (Magliozzi et al., 2018). This type of cortical lesion appears, based on pathology studies, to be highly specific, and can be extensive (Bo et al., 2003).

However, subpial demyelination goes largely undetected even with advanced MRI techniques at standard field strengths. Ultra-high field imaging with T2* (Mainero et al., 2009, 2015; Pitt et al., 2010) or MP2RAGE (Beck et al., 2018) sequences improves the visualization (Kilsdonk et al., 2016; Beck et al., 2018), but cannot be applied routinely in the clinical setting. Moreover, standardization with updated guidelines for identifying these types of cortical lesion are yet to be established.

Smoldering/slowly evolving lesions

Pathological studies show that up to 57% of chronic multiple sclerosis lesions are active or mixed (active and inactive) (Frischer et al., 2015; Kuhlmann et al., 2017; Luchetti et al., 2018). These lesions may be characterized by a slow rate of increase in size and ongoing tissue loss and are more common in cases with long disease duration and progressive multiple sclerosis phenotypes and are termed smoldering or slowly evolving/expanding lesions. Pathologically, they are typified by a ‘rim’ of iron-laden microglia and/or macrophages with altered morphology, activated microglia and macrophages at the edge, few T cells, and slow rate of ongoing demyelination and axonal loss (Frischer et al., 2015; Dal-Bianco et al., 2017; Kuhlmann et al., 2017; Luchetti et al., 2018).

Recently, these slowly evolving lesions have been investigated in vivo with MRI. Susceptibility-based MRI identifies a hypointense rim in some white matter multiple sclerosis lesions that may reflect activity detected with pathology in the periphery of lesions. This rim can persist over years (Bian et al., 2013; Absinta et al., 2016a; b; Dal-Bianco et al., 2017; Chawla et al., 2018; Filippi et al., 2019),
although it can also gradually disappear, returning to contrast similar to normal-appearing white matter after some years (Chen et al., 2014).

This hypointense rim is characteristic of lesions showing significant enlargement over time (Dal-Bianco et al., 2017), although expansion at the edge can be concurrent with volume loss within the lesion (Sethi et al., 2017) or no volume change (Bian et al., 2013).

Although T_{2*} and phase images at high-field hold promise for identifying smoldering/slowly evolving lesions, at present there is no consensus about the best technique for use in vivo. A method based on the automatic detection of these lesions on conventional brain T_{2*} and T_{1}-weighted images has been proposed recently (Elliott et al., 2018).

Interestingly, while slowly evolving lesions are common in multiple sclerosis, they are not found in neuromyelitis optica spectrum disorders (Sinnecker et al., 2012; Chawla et al., 2016), or in cerebrovascular diseases (Kilsonen et al., 2014).

Although the evaluation of a peripheral rim could be a promising characteristic to distinguish lesions suggestive of multiple sclerosis from other conditions, its role in the diagnostic work-up of patients with clinically isolated syndromes is still unknown. Further research is required before integration into diagnostic criteria, including the assessment of sensitivity and specificity, standardizing the appropriate MRI protocols and establishing the corresponding guidelines.

**Conclusions**

Focal white matter lesions, which are hyperintense on T_{2}-weighted scans, are among the pathological hallmarks of multiple sclerosis, and MRI is formally included in the diagnostic work-up of patients with suspected multiple sclerosis (McDonald et al., 2001). Current MRI criteria for multiple sclerosis are based on imaging features that are characteristic of the disease, but are not sufficiently specific. Over time, revisions of the multiple sclerosis diagnostic criteria have improved the sensitivity, particularly adding the capability to confirm the diagnosis at first clinical presentation.

However little attention has been given to describing the imaging features included in these criteria in detail, and guiding neurologists and neuroradiologists in correctly interpreting them. In patients with few lesions, there is a particularly increased risk of misdiagnosis based on MRI. We hope that the guidelines provided will minimize the risk of inappropriate image interpretation and increase the awareness of redflags.

As mentioned earlier, these criteria should only be used in the appropriate clinical context, when onset is characterized by clinical manifestations typical of multiple sclerosis.

Different scanners and field strengths, upgrades in equipment, and changes in acquisition parameters could influence lesion evaluations. However, although high-field MRI enables the detection of a higher number of white matter lesions in CIS and multiple sclerosis patients (Wattjes et al., 2006), field strength has been shown not to affect fulfillment of criteria for dissemination in space and time, also in a multicentre setting (Wattjes et al., 2008; Hagens et al., 2018).

Accordingly, if MRI studies are performed on scanners with a minimum field strength of 1.5 T and the MRI protocols are standardized using appropriate sequences to obtain good quality images with adequate resolution, lesion assessment and longitudinal monitoring can be performed robustly and independently of these confounding factors.

In challenging situations (e.g. low numbers of lesions and with confounding comorbidities) both the specific characteristics of each individual lesion as well as the overall patterns of lesions (e.g. symmetric central lesion in the pons and deep white matter lesions in ischaemic small-vessel disease) should be taken into account to support the diagnosis of multiple sclerosis or other conditions.

Emerging data suggest that advanced MRI sequences can enhance our ability to distinguish key, previously established characteristics of multiple sclerosis (e.g. cortical or perivenular lesions) that will enhance diagnosis because they are highly specific.

Although we focused the discussion on the 2017 revision of the McDonald criteria framework, the technical developments, combined with recent discoveries about the links between lesion characteristics and multiple sclerosis pathogenesis, will likely drive future improvements to—and perhaps ever rethinking of—current criteria.

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Supplementary material

Supplementary material is available at Brain online.

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