EFNS guidelines on the use of neuroimaging in the management of multiple sclerosis

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\textbf{Keywords:} diagnosis, MRI, multiple sclerosis, prognosis

Magnetic resonance (MR)-based techniques are widely used for the assessment of patients with suspected and definite multiple sclerosis (MS). However, despite the publication of several position papers, which attempted to define the utility of MR techniques in the management of MS, their application in everyday clinical practice is still suboptimal. This is probably related, not only, to the fact that the majority of published guidelines focused on the optimization of MR technology in clinical trials, but also to the continuing development of modern, quantitative MR-based techniques, that have not as yet entered the clinical arena. The present report summarizes the conclusions of the ‘EFNS Expert Panel of Neuroimaging of MS’ on the application of conventional and non-conventional MR techniques to the clinical management of patients with MS. These guidelines are intended to assist in the use of conventional MRI for the diagnosis and longitudinal monitoring of patients with MS. In addition, they should provide a foundation for the development of more widespread but rational clinical applications of non-conventional MR-based techniques in studies of MS patients.

\section*{Introduction}

Conventional magnetic resonance imaging (cMRI) has proven to be sensitive for detecting multiple sclerosis (MS) lesions and their changes over time [1,2]. This exquisite sensitivity has made cMRI the most important paraclinical tool in diagnosing MS and establishing a prognosis at the clinical onset of the disease. These are the main reasons why cMRI findings have a major role in the recently developed International Panel (IP) diagnostic criteria for MS [3]. Many research groups have subsequently taken steps to validate and refine these recommendations [4–8]. However, for clinicians, it remains unclear how and when cMRI should be used, not only at disease onset, but also during the subsequent disease phases. In addition, despite the sensitivity of cMRI for detecting MS lesions, the correlation between cMRI metrics (i.e. hyperintense lesions on T2- and post-contrast T1-weighted images, hypointense lesions on T1-weighted images, and atrophy measurements) and clinical findings of MS is still limited [1]. Amongst the likely reasons for this clinical/MRI discrepancy, a major one is the low pathological specificity of the abnormalities seen on cMRI scans and the inability of cMRI metrics to detect and quantify the extent of damage in normal-appearing brain tissues (NABTs) [1,9]. These inherent limitations of cMRI have prompted the development and application of modern quantitative MR techniques [MR spectroscopy (\textsuperscript{1}H-MRS), magnetization transfer (MT) MRI, diffusion-weighted (DW) MRI and functional MRI (fMRI)] to the study of MS. Although these techniques have provided important insight into the pathobiology of MS, their practical value in the assessment of MS patients in clinical practice has yet to be realized.
Aim of the European Federation of Neurological Science Task Force

The aim of the ‘European Federation of Neurological Science (EFNS) Expert Panel of Neuroimaging of MS’ is to define guidelines for the application of conventional and non-conventional MR techniques for the diagnosis and monitoring of patients with MS in clinical practice. In addition, they should clarify the current status and clinical role of non-conventional MR techniques.


MRI assessment of patients at presentation with clinically isolated syndromes suggestive of MS

In about 85% of patients with MS, the clinical onset of the disease is a clinically isolated syndrome (CIS) involving the optic nerve, brainstem or spinal cord [10]. Approximately 50–80% of these patients already have lesions on cMRI, consistent with prior disease activity [11–14]. As recent randomized controlled trials [15–17] have shown a treatment effect in patients with a CIS and MRI abnormalities suggestive of MS, it has become critical to expedite the identification of those patients at high risk a multiphasic inflammatory demyelinating disorder consistent with MS. Equally compelling has been the desire to characterize those factors that have the ability to prospectively predict which patients will be at highest risk for precocious and substantial disability accrual.

Conventional MRI

All of the diagnostic criteria proposed for MS [3,18,19] require the demonstration of disease dissemination in space and time. The central principal advanced in each of these diagnostic schemes involves the confirmation of two or more clinical attacks, separated in time, which involve at least two distinct areas of the central nervous system (CNS). Another key requirement in each of the diagnostic criteria is the exclusion of alternative diagnostic considerations that can mimic MS by appropriate tests. The Poser criteria, published in 1983, were the first set of criteria that integrated findings from para-clinical and laboratory tests [including cerebrospinal fluid (CSF) analysis, evoked potentials (EP) and MRI] to demonstrate spatial dissemination of the disease and to increase diagnostic confidence.

A critical feature in the diagnostic evaluation of patients suspected of having MS is the characterization of lesions profiles, that are suggestive of the disease. Brain MS lesions are frequently located in the periventricular regions, the corpus callosum and infratentorial areas (with the pons and cerebellum more frequently affected than the medulla and midbrain), and are characterized by oval or elliptical shapes [20]. In addition, consensus has been reached on criteria useful to identify T2 hyperintense [21] and T1-enhancing lesions [22]. As MS frequently affects the spinal cord, some characteristics of MS cord lesions have also been identified. Cord MS lesions are more frequently observed within the cervical than in the thoracic regions, are usually peripheral, limited to two vertebral segments in length or less, occupy less than half the cross-sectional area of the cord, and are not seen as T1-hypointensities [23]. Acute plaques typically produce swelling of the cord and enhancement after gadolinium (Gd) administration [24,25].

The optic nerve is also frequently involved in the course of MS. When an optic neuritis (ON) is suspected to be the onset manifestation of MS, the principal role of MRI is to assess the brain for asymptomatic lesions [14,26–28], whereas optic nerve MRI can be useful in ruling out alternative diagnosis. The sensitivity of MRI for detecting optic nerve lesions in patients with ON is high: a seminal study using a short-tau inversion recovery (STIR) sequence showed lesions in 84% of symptomatic nerves and 20% of asymptomatic nerves [29]. The use of fat-saturated fast spin echo [30] and selective partial inversion recovery pre pulse (SPIR)-FLAIR [31] sequences have led to increases in sensitivity for detecting lesions in patients with an ON. In MS patients, increased T2 signal can be seen long time after an episode of ON, despite improvements in vision and visual EP, and even in the absence of acute attacks of ON [32]. T1-hypointense lesions are not seen in the optic nerve [23], whereas Gd enhancement is a consistent feature of acute ON [33,34].

In the past two decades, a number of MRI criteria have been proposed [12,35,36] to increase the confidence in rendering a diagnosis of MS:

- Criteria of Paty et al. [36]: presence of at least four T2-hyperintense lesions, or three T2 lesions, of which one is periventricular. These criteria are characterized by high sensitivity but relatively low specificity [37] (class I evidence).
- Criteria of Fazekas et al. [35]: presence of at least three T2-hyperintense lesions with two of the following characteristics: an infratentorial lesion, a
periventricular lesion, and a lesion larger than 6 mm. These criteria showed both high sensitivity and high specificity when evaluated retrospectively in definite MS [38], but have limited predictive value when applied prospectively in patients with CIS [39] (class II evidence).

- Criteria of Barkhof et al. [12]: presence of at least three of the four following features: presence of at least one Gd-enhancing lesion, at least one juxta-cortical lesion, at least one infratentorial lesion and three or more periventricular lesions (class I evidence). In 2000, Tintoré et al. [40] slightly modified these criteria by allowing for nine T2 lesions to be an alternative for the presence of an enhancing lesion and reported a high specificity of these criteria to predict conversion from CIS to clinically definite (CD) MS (class I evidence).

In the most recent diagnostic criteria [3] proposed by an IP of MS specialists, demonstration of dissemination in space was based on the modified Barkhof–Tintoré criteria. For the first time, these criteria underpinned the role of spinal cord lesions in demonstrating disease dissemination in space. When these more stringent imaging criteria are not fulfilled, the IP criteria allow the presence of at least two T2 lesions when oligoclonal bands are detected in the CSF. However, Tintoré et al. [7] recently showed that this alternative criterion may result in a decreased diagnostic accuracy, as they reported in CIS patients followed for 3 years a specificity of only 63% for the development of CDMS (class III evidence). In the IP criteria [3], temporal dissemination can be demonstrated either by the presence of at least one enhancing lesion on an MRI scan performed 3 months or more after the onset of the clinical event or by the presence of one new T2 or enhancing lesion on an MRI scan performed 6 months or more after the onset of the clinical event (only if there is a previous scan at least 3 months after the event in case of a T2 lesion).

The major advantage of the IP criteria [3] is that they facilitate the early diagnosis of MS in patients with a clinically isolated attack before a second clinical relapse has occurred. In a 3-year follow-up study of CIS patients, Dalton et al. [5] showed a sensitivity, specificity and accuracy of 83% of the IP criteria to predict conversion to CDMS (class III evidence). These results were confirmed by Tintoré et al. [7], who reported a sensitivity of 74%, specificity of 86%, and accuracy of 80% (class III evidence). In the placebo arm of a trial of patients at the earliest clinical stage of MS, the IP criteria for dissemination in space were similarly effective in predicting subsequent evolution to CDMS [4] (class II evidence). However, it is worth noting that the MRI spatial dissemination criteria are less specific in predicting conversion to CDMS when applied to patients presenting with a CIS of the brain stem [41] (class II evidence). The presence of asymptomatic cord lesions was helpful in demonstrating spatial dissemination in recently diagnosed MS patients [42] (class IV evidence), but the substitution of a brain lesion with a cord lesion did not impact significantly on the subsequent diagnosis in patients presenting with ON [43] (class III evidence). When a new T2 lesion was allowed as evidence for dissemination in time, one study showed that 82% of CIS patients who fulfilled the IP MRI criteria for MS after 3 months had developed CDMS within 3 years [44] (class III evidence), and another found that 80% of those CIS who fulfilled the same criteria after 1 year developed CDMS within 3 years [7] (class III evidence).

Several authors have investigated the prognostic role of MR-derived metrics in patients presenting with CIS. The MRI findings that showed the strongest predictive value for the subsequent development of definite MS on short- to medium-term follow up, were the number and extent of T2-visible brain lesions at disease onset [11,13,14,45] (class II evidence), the presence of infratentorial lesions [45] (class III evidence) and the presence of Gd-enhancing lesions [12,15].

During the last decades, several quantitative MR techniques have been developed for the assessment of brain damage in patients with MS. Even if the application of these techniques in everyday clinical practice is, at the moment, still premature, as these techniques often require dedicated personnel and specific softwares for the analysis, it is likely that with their progressive availability their use in clinical practice will increase.

The progressive development of brain and spinal cord atrophy is a well-known radiographic feature of MS [46,47]. Objective quantification of CNS atrophy has been recognized as a potentially useful marker of the destructive and irreversible components of MS-related tissue damage. Recent MRI studies have confirmed that irreversible tissue loss/damage occurs early in the course of the disease and it is likely that the extent of such irreversible tissue damage conveys important prognostic information. Three studies [48–50] showed the development of regional or global brain atrophy over a period of up to 3 years in CIS patients who evolved to MS. In one of these studies [49], progressive gray matter atrophy in the brain was also observed. A recent study has shown that in CIS patients a low dose of interferon (IFN)-β-1a given subcutaneously once a week reduces the rate of brain atrophy by about 30% over 2 years [50]. On the contrary, compared with normal controls, cord area was found to be only slightly reduced in patients presenting with CIS and an abnormal MRI scan, and cord area remained stable over 1 year after disease onset [51].
Non-conventional MRI

**MT-MRI**
Reduced MT ratio (MTR) values have been detected in the NABT from patients at presentation with CIS [52,53]. The extent of these abnormalities appears to be an independent predictor of subsequent disease evolution [52]. However, these observations were not confirmed by later studies [54,55]. No abnormalities have been detected in the cervical cord of CIS patients using this technique [56].

**DT MRI**
DT MRI has disclosed subtle abnormalities in the normal-appearing white matter (NAWM) of patients at presentation with CIS [57]. However, these abnormalities were found not to be predictive of temporal lesion dissemination in time (as defined by McDonald criteria) at 3 and 12 months [7].

**$^1$H-MRS**
Metabolic abnormalities, consisting in a reduction of the concentration of N-acetylaspartate (NAA) of the whole brain [58] and in an increase of myo-inositol (mI) and creatine (Cr) in NAWM [59] have been shown in patients at the earliest clinical stage of MS. These findings suggest that widespread axonal pathology, glial injury and an increase in cell turnover or metabolism are rather early phenomenon in the course of the disease.

**Functional MRI**
Using fMRI, an abnormal pattern of movement-associated cortical activation has also been described in CIS patients within 3 months from disease onset [60,61]. In a 1-year follow-up study of CIS patients [62], those who developed CDMS had a different motor fMRI response at first presentation when compared with those who did not, suggesting that, in CIS patients, the extent of early cortical reorganization following tissue injury might be a factor associated with a different disease evolution.

**Recommendations**
In patients at presentation with CIS suggestive of MS (i.e. neurological findings typically seen in the setting of MS) [6], after appropriate exclusion of alternative diagnostic considerations that can mimic MS, the following recommendations should be considered:

1. cMRI of the brain (dual-echo, pre- and post-contrast T1-weighted scans) should be obtained as soon as possible in all patients presenting with an isolated demyelinating syndrome involving the CNS, not only to collect additional evidence for lesion dissemination in space, but also to exclude other possible neurological conditions. As suggested by recent guidelines from the American Academy of Neurology [6], the finding in these patients of three or more T2-hyperintense lesions with the imaging characteristics underlined by the IP guidelines [3] (Type A recommendation) and the presence of two or more Gd-enhancing lesions at baseline are sensitive predictors of the subsequent development of CDMS within the next 7–10 years (Type B recommendation).

2. The presence of three or more white matter lesions on brain T2-weighted MRI in patients suspected of having MS is not diagnostic, especially when their location and appearance is non-characteristic for demyelination. In this context the IP criteria [3] should be applied. Incidental white matter lesions are not an infrequent observation even in the young normal population. Note that with ageing (at least > 50 years) incidental white matter lesions may also show progression [63,64] (good practice point).

3. In the case of steroids treatment, which is known to dramatically suppress Gd enhancement, one of the possible markers of inflammation, cMRI should be performed before treatment or, at least, 1 month after treatment termination (good practice point).

4. cMRI of the spinal cord is useful in those circumstances when brain MRI is normal or equivocal, and in patients with non-specific brain T2-abnormalities (especially when older than 50 years), because, contrary to what happens for the brain, cord lesions rarely develop with ageing per se [65]. In patients presenting with a spinal cord syndrome, spinal cord MRI is highly recommended to rule out other conditions that may mimic MS, such as compressive lesions (good practice point).

5. In patients with acute ON, MRI of the optic nerve can be useful in ruling out alternative diagnosis. In this case, STIR sequences should be used (good practice point).

6. Follow-up MRIs are required to demonstrate disease dissemination in time. In this perspective, the appearance of Gd-enhancing lesions 3 months after the clinical episode (and after a baseline MRI assessment) or new T2- or Gd-enhancing lesions 6 months after the clinical episode (and after a baseline MRI assessment) is highly predictive of the subsequent development of definite MS in the near term [6] (Type A recommendation). Follow-up scans need to be performed with the same machinery and scanning parameters and identical slice positions are required for exact comparison.

7. Repeat scanning beyond the two initial studies need to be considered by individual neurologists considering the clinical circumstances that are appropriate for each patient (is not routinely recommended as the
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8. Even though non-conventional MRI techniques may provide essential and critical information in patients with CIS and their application for monitoring treatment might provide a more accurate assessment of efficacy on inflammation, axonal protection and demyelination/remyelination, their use in clinical practice is, currently, not recommended. All these techniques are yet to be adequately compared with cMRI for sensitivity and specificity in detecting tissue damage in MS and for predicting the development of MS and disability. At present, these quantitative techniques show differences at a group level, but do not allow inferences at an individual level.

9. In patients with insidious neurological progression suggestive of MS, according to published criteria [67] an abnormal CSF findings with evidence of inflammation and immune abnormality is another important finding to corroborate the diagnostic suspicion.

**MRI in patients with established MS**

In patients with relapsing–remitting (RR) and secondary progressive (SP) MS, disease activity is detected five to 10 times more frequently on cMRI scans than with clinical assessment of relapses [68]. This coupled with the fact that cMRI provides objective and sensitive measures of disease activity, led to the use of cMRI as an established tool for assessing the natural history of MS progression and for monitoring response to treatment. In clinical trial context, cMRI is used as a primary outcome measure in phase II studies, where serial scans (usually monthly) are acquired to detect disease activity (new or enlarged T2 lesion counts, total enhancing and new enhancing lesion counts and enhancing lesion volume) [69]. In phase III trials, given the uncertainty of cMRI in predicting clinical benefit, surrogate imaging methods are used as secondary outcome measures to detect disease progression, usually on yearly scans, specifically in terms of increase in total T2-hyperintense lesion load [70].

**Conventional MRI**

The cMRI sequences typically used for studying MS patients are dual-echo and post-contrast T1-weighted scans. Lesion burden on T2 MRI increases by 5–10% per year [71]. Several cross-sectional studies evaluated differences in T2 lesion load amongst different MS phenotypes. T2 lesion load is higher in SPMS in comparison with benign [72,73], RRMS and primary progressive (PP) MS [72]. However, the magnitude of the correlation between T2-lesion measures and disability within various disease phenotypes in cross-sectional studies has been rather disappointing [74–77]. This poor relationship is likely related to the many limitations of the clinical scales used to measure impairment and disability in MS and to the inability of cMRI to characterize and quantify the extent and severity of MS pathology beyond T2-visible lesions [78]. Furthermore, it has recently been demonstrated a plateauing relationship between dual-echo lesion load and disability, indicating that, for EDSS higher than 4.5, metrics different from T2-lesion loads should be taken into account [79]. Serial MRI studies have shown that enhancement occurs in almost all new lesions in patients with RRMS or SPMS [80,81] and can be sometimes detected even before the onset of clinical symptoms [82]. The burden of MRI activity can be stratified on the basis of clinical phenotype, being higher in RRMS [83] and SPMS [84] in comparison with PPMS [84] and benign MS [83]. It is conspicuous that severely disabled SPMS patients exhibit a substantially lower incidence of enhancing lesions when compared with those with mildly disabled RRMS [85]. Several studies have investigated the prognostic role of enhancing MRI on corresponding clinical parameters. The number of enhancing lesions increases shortly before and during clinical relapses and predicts subsequent MRI activity [86–89]. A moderate correlation has been demonstrated between the degree of clinical disability and the mean frequency of enhancing lesions in patients with RRMS [90] and SPMS [91].

A rigorous and valid strategy for the MR-based longitudinal monitoring of MS (either natural or modified by treatment) must involve the use of standardized imaging protocols (including consistency in slice thickness and imaging planes, field strength, and patient repositioning). Several guidelines have emphasized the importance of accurate patient positioning inside the magnet in order to define landmarks for achieving effective coregistration on serial scans. Such procedures facilitate the accurate interpretation of follow-up studies. Several reviews provide detailed analysis of the advantages and disadvantages of the application of different pulse sequences for characterizing the disease burden in MS [70,76]. In addition, considering the importance of active lesion detection for assessing disease activity, several strategies have been suggested to increase enhancing lesion detection, including increasing post-injection delay, increasing Gd dose, and the application of MT saturation pulses to reduce background signal and increase lesion identification [9,92]. However, despite the increased sensitivity of these strategies [9,92], the application of higher doses of Gd and MT pulsing in the routine assessment of MS patients is still not advisable because of an unfavorable
cost–benefit ratio. However, there is general agreement that an interval of 5–7 min between the injection of contrast material and the acquisition of post-contrast sequences should be used routinely to optimize the sensitivity and create standardization within and between centers [93].

Over the past decade, a large number of parallel group, placebo-controlled and baseline-versus-treatment trials have clearly shown the ability of several immunomodulating and immunosuppressive treatments to reduce both MRI-measured inflammation and the consequent increase of accumulated lesion burden in patients with CIS [15–17] (class I evidence), RRMS [94–101] (class I evidence) and SPMS [102–104] (class I evidence). Recently, the long-term effects of some of these treatments on MRI-accumulated disease burden have also been documented [105–107] (class I evidence). Two different studies, conducted on patients treated with IFN-β-1a, have recently explored whether MRI disease activity measured with Gd or new T2 lesions at the beginning of the treatment identifies better subsequent IFN-β therapeutic response than clinical activity [108,109] (class I evidence). Even if these data suggest that MRI classification may facilitate rational therapeutic decisions, they need to be replicated before being applied in clinical practice. Persistently hypointense lesions on enhanced T1-weighted images (known as ‘black holes’) correspond to areas where chronic severe tissue disruption has occurred. At present, there is a general tendency to consider the assessment of the extent of chronic black holes as a surrogate marker to monitor MS evolution. T1-hypointense lesion load is higher [110–113] and increases more rapidly over time in SPMS and PPMS than in RRMS [103,112]. Cross-sectional [110,112,114–116] and longitudinal studies [103,117] have shown that T1-hypointense lesion load correlates better with clinical disability than T2-lesion load, particularly in SPMS patients.

A few trials have investigated the effect of treatment in preventing the accumulation of T1 black holes [118–121] in RRMS and SPMS and have consistently shown that the effect, if any, of all the tested treatments in reducing the rate of accumulation of black holes was moderate at best. Several studies have also evaluated the effects of available treatments, [122–124], on the probability of newly formed MS lesions to evolve into chronically T1 hypointense lesions. Although this approach is highly time-consuming, it is promising for assessing in a relatively short time the ability of a given treatment to favorably alter the mechanisms leading to irreversible tissue loss.

Measurement of brain and cord atrophy has also been applied to assess the extent of tissue loss in MS [46]. In MS patients with different disease phenotypes, on average, brain volume decreases by about 1% yearly [46], despite evidence of highly variable disease activity. Although it appears to be more pathologically specific than T2 lesion load, brain atrophy is at best only moderately correlated with disability in RRMS and SPMS [46,125,126]. The strength of the correlation increases when neuropsychological impairment is considered [125] and with a longitudinal study design [127, 128]. Also, in patients with MS, particularly in those with the progressive phenotypes of the disease, changes at a given time point and over time of cord cross-sectional area correlate better with clinical disability than changes in cord T2-visible lesions [117,129].

Alternatively, good correlations have recently been found between regional brain atrophy and disability in MS patients. Cross-sectional studies [130,131] demonstrated gray matter atrophy in early RRMS. In addition, brain atrophy appears to evolve by involving different structures in different phases of the disease, being ventricular enlargement predominant in RRMS, and cortical atrophy more important in the progressive forms of the disease [132]. Furthermore, regional brain atrophy shows a better correlation with cognitive impairment than global atrophy or T1 and T2 lesion assessments [133,134].

As shown for T1-hypointense lesions, the effect of treatment in preventing the development of brain atrophy in patients with RRMS and SPMS was at most moderate and not seen at all in some studies [88,103,107,135–140]. In order to refine the reproducibility of brain atrophy measurements, several recommendations have been provided [46,140,141], including: (1) the acquisition of 3D T1-weighted sequences; (2) the use of automated segmentation algorithms for images segmentation; (3) the development of a quality assurance program to confirm the stability of the measurement system over time.

Non-conventional MRI

MT-MRI, DT-MRI and ¹H-MRS provide quantitative and continuous measures that can assess global (whole brain), specific CNS structures, including the optic nerve and spinal cord, and various compartments (i.e. macroscopic lesions, NABT, NAWM, and gray matter) [1,78]. Using these techniques, microscopic abnormalities beyond the resolution of cMRI have been detected in patients with different disease phenotypes and have been shown to correlate better with the degree of disability and cognitive impairment than cMRI measures [1,78]. Longitudinal studies have shown significant worsening of non-conventional MRI metrics over time in MS patients. These techniques provide useful prognostic information for the medium-term clinical disease evolution [142].
Several recent MS clinical trials have incorporated MT-MRI to assess the impact of treatment on demyelination and axonal loss. MT-MRI has been used in phase II and phase III trials for RRMS (injectable and oral IFN-β-1a, IFN-β-1b, oral GA) [143–145] and SPMS (IFN-β-1b and immunoglobulins) [146,147]. The studies on RRMS patients were conducted at single centers with a small number of patients, and, as a consequence, they were not confronted with problems of standardization of MT acquisition and post-processing. In contrast, those conducted on SPMS patients included larger sample of patients, recruited in several centers. The results of these multicenter trials have shown a lack of an effect of IFN-β-1b [146] and intravenous immunoglobulins [147] on MT-MRI-derived quantities of the whole-brain tissue and NAWM from SPMS patients.

An International consensus conference of the White Matter Study Group of the International Society for MR in Medicine has provided several guidelines for using MT-MRI for monitoring treatment in MS [148]. Amongst the suggestions provided in these guidelines, it is recommended the use of scanners with field strength of 1.5 T, gradient-echo sequences and the standardization of magnetization saturation amongst centers. Corrections for scanner properties like variations in the B1 field may also serve to reduce the variability of MT measurements between sites [149]. Quality assurance procedures and centralized analysis of the data represent additional important requirements.

1H-MRS studies are relatively technically challenging and time-consuming and require calibration amongst centers, post-processing, and information from cMRI, as well as knowledgeable and experienced personnel. As a consequence, high-quality 1H-MRS technology and operators are still confined to relatively few centers. Sampling and reposition errors and scanner drift are also likely to occur in serial studies. This inevitably reduces the reproducibility of 1H-MRS measures. The use of whole-brain NAA measurements overcomes these limitations, at the price of loosing information on specific brain regions or tract systems [150]. Preliminary studies have been conducted to evaluate the effect of disease-modifying treatments on 1H-MRS-derived parameters [151–155].

Recently, Narayana et al. [156] demonstrated the feasibility of applying 1H-MRS in multicenter clinical trials of MS, by showing the between-centers stability of NAA/Cr ratios.

Recommendations

In patients with established MS, the following recommendations should be considered:

1. cMRI scans (dual-echo and post-contrast T1-weighted images) should be obtained using standardized protocols and accurate procedures for patients' repositioning in order to facilitate the interpretation of follow-up studies. Post-contrast T1-weighted scans should be acquired after an interval of 5–7 min from the injection of contrast material [93]. Considering the weak correlation with clinical finding and the low predictive value of cMRI metrics for the subsequent worsening of clinical disability, the use of surveillance MRI for the purpose of making treatment decisions cannot be generally recommended [93]. Serial MRI scans should be considered when diagnostic issues arise.

2. Repetition of MRI of the spinal cord is advisable only if suspicion arises concerning the evolution of an alternate process (e.g. mechanical compression) or atypical symptoms develop.

3. Although preliminary work based on clinical trial data has suggested that presence [108] and amount [109] of MRI-detected disease activity may identify IFN-β response status in terms of relapse rate [108] and accumulated disability [109] in MS patients at a group level, there are no validated methods for monitoring disease-modifying therapy in individual patients.

4. Metrics derived from cMRI are not enough to provide a complete picture of the MS pathological process. Although cMRI has undoubtedly improved our ability to assess the efficacy of experimental MS therapies and, at least partially, our understanding of MS evolution, it provides only limited information on MS pathology in terms of accuracy and specificity and it has limited correlations with clinical metrics. This implies that the ability of a given treatment to modify metrics derived from cMRI does not mean that the treatment will necessarily be able to prevent the progressive accumulation of clinical disability, especially at an individual patient level.

5. Measurements of T1-hypointense lesions loads and brain and cord atrophy in clinical practice continue to be considered at a preliminary stage of development, as they need to be standardized in terms of acquisition and post-processing. Conversely, these metrics should be included as an end-point in disease-modifying agents trials [46], in order to further elucidate the mechanisms responsible for disability.

6. The application of non-conventional MRI techniques in monitoring patients with established MS in clinical practice is, at the moment, not advisable. All these techniques still need to be evaluated for sensitivity and specificity in detecting tissue damage in MS and its changes over time.

7. MT-MRI should be incorporated into new clinical trials to gain additional insights into disease patho-
physiology and into the value of this technique in the assessment of MS. The performance and contribution of DT-MRI and 1H-MRS in multicenter trials still have to be evaluated.

Conflict of interest

These guidelines are provided as an educational service of the EFNS task force. It is based on current scientific and clinical information.

Acknowledgements

We are grateful to Prof. D. H. Miller (Institute of Neurology, London, UK) for his helpful and thoughtful comments to the manuscript.

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