

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

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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.

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 (¹H-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.

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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.

Search strategy: data for this review were identified by searches of Medline and references from relevant articles from 1965 to 2005. The search terms 'Multiple Sclerosis', 'Magnetic Resonance Imaging', 'Diagnosis', 'Prognosis', 'Atrophy', 'Magnetization Transfer MRI', 'Diffusion Weighted MRI', 'Diffusion Tensor MRI', 'Proton Magnetic Resonance Spectroscopy', 'Disability' and 'Treatment' were used. Only papers published in English were reviewed.

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 juxtacortical lesion, at least one infratentorial lesion and three or more periventricular lesions (class I evidence). In 2000, Tintorè 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–Tintorè 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, Tintorè 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 Tintorè 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 pre-

dicting 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].

¹H-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

disease becomes more likely to manifest clinically in the longer term [5,66] (good practice point).

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].

Alternately, 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 B_1 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 losing 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.

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References

- Filippi M, Rocca MA, Comi G. The use of quantitative magnetic-resonance-based techniques to monitor the evolution of multiple sclerosis. *Lancet Neurology* 2003; **2**: 337–346.
- Bakshi R, Hutton GJ, Miller JR, Radue EW. The use of magnetic resonance imaging in the diagnosis and long-term management of multiple sclerosis. *Neurology* 2004; **63**: S3–S11.
- McDonald WI, Compston A, Edan G, *et al.* Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of Neurology* 2001; **50**: 121–127.
- Barkhof F, Rocca M, Francis G, *et al.* Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon beta1a. *Annals of Neurology* 2003; **53**: 718–724.
- Dalton CM, Brex PA, Miszkil KA, *et al.* Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis. *Annals of Neurology* 2002; **52**: 47–53.
- Frohman EM, Goodin DS, Calabresi PA, *et al.* The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2003; **61**: 602–611.
- Tintoré M, Rovira A, Rio J, *et al.* New diagnostic criteria for multiple sclerosis: application in first demyelinating episode. *Neurology* 2003; **60**: 27–30.
- Polman CH, Wolinsky JS, Reingold SC. Multiple sclerosis diagnostic criteria three years later. *Multiple Sclerosis* 2005; **11**: 5–12.
- Rovaris M, Filippi M. Magnetic resonance techniques to monitor disease evolution and treatment trial outcomes in multiple sclerosis. *Current Opinion in Neurology* 1999; **12**: 337–344.
- Noseworthy JH, Lucchinetti C, Rodriguez M, Weinstenker BG. Multiple sclerosis. *New England Journal of Medicine* 2000; **343**: 938–952.
- Filippi M, Horsfield MA, Morrissey SP, *et al.* Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. *Neurology* 1994; **44**: 635–641.
- Barkhof F, Filippi M, Miller DH, *et al.* Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 1997; **120**: 2059–2069.
- O’Riordan JI, Thompson AJ, Kingsley DP, *et al.* The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. *Brain* 1998; **121**: 495–503.
- Brex PA, Ciccarelli O, O’Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *New England Journal of Medicine* 2002; **346**: 158–164.
- Jacobs L, Beck R, Simon J, *et al.* Intramuscular interferon beta-1a therapy initiated during the first demyelinating event in multiple sclerosis. *New England Journal of Medicine* 2000; **343**: 898–904.
- Comi G, Filippi M, Barkhof F, *et al.* Effect of early interferon treatment on conversion to definite multiple sclerosis. *Lancet* 2001; **357**: 1576–1582.
- Achiron A, Kishner I, Sarova-Pinhas I, *et al.* Intravenous immunoglobulin treatment following the first demyelinating event suggestive of multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Archives of Neurology* 2004; **61**: 1515–1520.
- Schumacher FA, Beeve GW, Kibler RF. Problems of experimental trails of therapy in multiple sclerosis. *Annals of the New York Academy of Science* 1965; **122**: 552–568.
- Poser CM, Paty DW, Scheinberg L, *et al.* New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology* 1983; **13**: 227–231.
- Ormerod IE, Miller DH, McDonald WI, *et al.* The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions. A quantitative study. *Brain* 1987; **110**: 1579–1616.
- Filippi M, Gawne-Cain ML, Gasperini C, *et al.* Effect of training and different measurement strategies on the reproducibility of brain MRI lesion load measurements in multiple sclerosis. *Neurology* 1998; **50**: 238–244.
- Barkhof F, Filippi M, van Waesberghe JH, *et al.* Improving interobserver variation in reporting gadolinium-enhanced MRI lesions in multiple sclerosis. *Neurology* 1997; **49**: 1682–1688.
- Gass A, Filippi M, Rodegher ME, Schwartz A, Comi G, Hennerici MG. Characteristics of chronic MS lesions in the cerebrum, brainstem, spinal cord, and optic nerve on T1-weighted MRI. *Neurology* 1998; **50**: 548–550.
- Tartaglino LM, Friedman DP, Flanders AE, Lublin FD, Knobler RL, Liem M. Multiple sclerosis in the spinal cord: MR appearance and correlation with clinical parameters. *Radiology* 1995; **195**: 725–732.
- Rocca MA, Mastrorlando G, Horsfield MA, *et al.* Comparison of three MR sequences for the detection of cervical cord lesions in patients with multiple sclerosis. *American Journal of Neuroradiology* 1999; **20**: 1710–1716.
- Optic Neuritis Study Group. The 5-year risk of MS after optic neuritis. Experience of the optic neuritis treatment trial. *Neurology* 1997; **49**: 1404–1413.
- Optic Neuritis Study Group. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis. Experience of the Optic Neuritis Treatment Trial. *Archives of Ophthalmology* 2003; **121**: 944–949.

28. Hickman SJ, Dalton CM, Miller DH, Plant GT. Management of acute optic neuritis. *The Lancet* 2002; **360**: 1953–1962.
29. Miller DH, Newton MR, van der Poel JC, *et al.* Magnetic resonance imaging of the optic nerve in optic neuritis. *Neurology* 1988; **38**: 175–179.
30. Gass A, Moseley IF, Barker GJ, *et al.* Lesion discrimination in optic neuritis using high-resolution fat-suppressed fast spin-echo MRI. *Neuroradiology* 1996; **38**: 317–321.
31. Jackson A, Sheppard S, Laitt RD, Kassner A, Moriarty D. Optic neuritis: MR imaging with combined fat- and water-suppression techniques. *Radiology* 1998; **206**: 57–63.
32. Davies MB, Williams R, Haq N, Pelosi L, Hawkins CP. MRI of optic nerve and postchiasmal visual pathways and visual evoked potentials in secondary progressive multiple sclerosis. *Neuroradiology* 1998; **40**: 765–770.
33. Kupersmith MJ, Alban T, Zeiffer B, Lefton D. Contrast-enhanced MRI in acute optic neuritis: relationship to visual performance. *Brain* 2002; **125**: 812–822.
34. Hickman SJ, Toosy AT, Jones SJ, *et al.* Serial magnetization transfer imaging in acute optic neuritis. *Brain* 2004; **127**: 692–700.
35. Fazekas F, Offenbacher H, Fuchs S, *et al.* Criteria for an increased specificity of MRI interpretation in elderly subjects with suspected multiple sclerosis. *Neurology* 1988; **38**: 1822–1825.
36. Paty DW, Oger JJ, Kastrukoff LF, *et al.* MRI in the diagnosis of MS: a prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. *Neurology* 1988; **38**: 180–185.
37. Lee KH, Hashimoto SA, Hooge JP, *et al.* Magnetic resonance imaging of the head in the diagnosis of multiple sclerosis: a prospective 2-year follow-up with comparison of clinical evaluation, evoked potentials, oligoclonal banding and CT. *Neurology* 1991; **41**: 657–660.
38. Offenbacher H, Fazekas F, Schmidt R, *et al.* Assessment of MRI criteria for a diagnosis of MS. *Neurology* 1993; **43**: 905–909.
39. Tas MW, Barkhof F, van Walderveen MA, Polman CH, Hommes OR, Valk J. The effect of gadolinium on the sensitivity and specificity of MR in the initial diagnosis of multiple sclerosis. *American Journal of Neuroradiology* 1995; **2**: 259–264.
40. Tintoré M, Rovira A, Martínez MJ, *et al.* Isolated demyelinating syndromes: comparison of different MRI criteria to predict conversion to clinically definite multiple sclerosis. *American Journal of Neuroradiology* 2000; **21**: 702–706.
41. Sastre-Garriga J, Tintore M, Rovira A, *et al.* Specificity of Barkhof criteria in predicting conversion to multiple sclerosis when applied to clinically isolated brainstem syndromes. *Archives of Neurology* 2004; **61**: 222–224.
42. Bot JC, Barkhof F, Lycklama a Nijeholt G, *et al.* Differentiation of multiple sclerosis from other inflammatory disorders and cerebrovascular disease: value of spinal MR imaging. *Radiology* 2002; **223**: 46–56.
43. Dalton CM, Brex PA, Miszkiel KA, *et al.* Spinal cord MRI in clinically isolated optic neuritis. *Journal of Neurology, Neurosurgery, and Psychiatry* 2003; **74**: 1386–1389.
44. Dalton CM, Brex PA, Miszkiel KA, *et al.* New T2 lesions enable an earlier diagnosis of multiple sclerosis in clinically isolated syndromes. *Annals of Neurology* 2003; **53**: 673–676.
45. Minneboo A, Barkhof F, Polman CH, Uitdehaag BM, Knol DL, Castelijns JA. Infratentorial lesions predict long term disability in patients with initial findings suggestive of multiple sclerosis. *Archives of Neurology* 2004; **61**: 217–221.
46. Miller DH, Barkhof F, Frank JA, Parker GJM, Thompson AJ. Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. *Brain* 2002; **125**: 1676–1695.
47. Lin X, Tench CR, Evangelou N, Jaspan T, Constantinescu CS. Measurement of spinal cord atrophy in multiple sclerosis. *Journal of Neuroimaging* 2004; **14**: 20S–26S.
48. Dalton CM, Brex PA, Jenkins R, *et al.* Progressive ventricular enlargement in patients with clinically isolated syndromes is associated with the early development of multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry* 2002; **73**: 141–147.
49. Dalton CM, Chard DT, Davies GR, *et al.* Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. *Brain* 2004; **127**: 1101–1107.
50. Filippi M, Rovaris M, Inglese M, *et al.* Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. *The Lancet* 2004; **364**: 1489–1496.
51. Brex PA, Leary SM, O’Riordan JI, *et al.* Measurement of spinal cord area in clinically isolated syndromes suggestive of multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry* 2001; **70**: 544–547.
52. Iannucci G, Tortorella C, Rovaris M, Sormani MP, Comi G, Filippi M. Prognostic value of MR and magnetization transfer imaging findings in patients with clinically isolated syndromes suggestive of multiple sclerosis at presentation. *American Journal of Neuroradiology* 2000; **21**: 1034–1038.
53. Traboulsee A, Dehmeshki J, Brex PA, *et al.* Normal-appearing brain tissue MTR histograms in clinically isolated syndromes suggestive of MS. *Neurology* 2002; **59**: 126–128.
54. Kaiser JS, Grossman RI, Polansky M, Udupa JK, Miki Y, Galetta SL. Magnetization transfer histogram analysis of monosymptomatic episodes of neurologic dysfunction: preliminary findings. *American Journal of Neuroradiology* 2000; **21**: 1043–1047.
55. Brex PA, Leary SM, Plant GT, Thompson AJ, Miller DH. Magnetization transfer imaging in patients with clinically isolated syndromes suggestive of multiple sclerosis. *American Journal of Neuroradiology* 2001; **22**: 947–951.
56. Rovaris M, Gallo A, Riva R, *et al.* An MT MRI study of the cervical cord in clinically isolated syndromes suggestive of MS. *Neurology* 2004; **63**: 584–585.
57. Gallo A, Rovaris M, Riva R, *et al.* Diffusion-tensor magnetic resonance imaging detects normal-appearing white matter damage unrelated to short-term disease activity in patients at the earliest clinical stage of multiple sclerosis. *Archives of Neurology* 2005; **62**: 803–808.
58. Filippi M, Bozzali M, Rovaris M, *et al.* Evidence for widespread axonal damage at the earliest clinical stage of multiple sclerosis. *Brain* 2003; **126**: 433–437.

59. Fernando KT, McLean MA, Chard DT, *et al.* Elevated white matter myo-inositol in clinically isolated syndromes suggestive of multiple sclerosis. *Brain* 2004; **127**: 1361–1369.
60. Rocca MA, Mezzapesa DM, Falini A, *et al.* Evidence for axonal pathology and adaptive cortical reorganization in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis. *NeuroImage* 2003; **18**: 847–855.
61. Filippi M, Rocca MA, Mezzapesa DM, *et al.* Simple and complex movement-associated functional MRI changes in patients at presentation with clinically isolated syndromes suggestive of MS. *Human Brain Mapping* 2004; **21**: 106–115.
62. Rocca MA, Mezzapesa DM, Ghezzi A, *et al.* A widespread pattern of cortical activations in patients at presentation with clinically isolated symptoms is associated with evolution to definite multiple sclerosis. *American Journal of Neuroradiology* 2005; **26**: 1136–1139.
63. Schmidt R, Enzinger C, Ropele S, Schmidt H, Fazekas F.; Austrian Stroke Prevention Study. Progression of cerebral white matter lesions: 6-year results of the Austrian Stroke Prevention Study. *The Lancet* 2003; **361**: 2046–2048.
64. Longstreth WT, Arnold AM, Beauchamp NJ Jr, *et al.* Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke* 2005; **36**: 56–61.
65. Kidd D, Thorpe JW, Thompson AJ, *et al.* Spinal cord MRI using multi-array coils and fast spin echo. II. Findings in multiple sclerosis. *Neurology* 1993; **43**: 2632–2637.
66. Miller DH, Filippi M, Fazekas F, *et al.* Role of magnetic resonance imaging within diagnostic criteria for multiple sclerosis. *Annals of Neurology* 2004; **56**: 273–278.
67. Thompson AJ, Montalban X, Barkhof F, *et al.* Diagnostic criteria for primary progressive multiple sclerosis: a position paper. *Annals of Neurology* 2000; **47**: 831–835.
68. McDonald WI, Miller DH, Thompson AJ. Are magnetic resonance findings predictive of clinical outcome in therapeutic trials in multiple sclerosis? The dilemma of interferon-beta. *Annals of Neurology* 1994; **36**: 14–18.
69. Barkhof F, Filippi M, Miller DH, Tofts P, Kappos L, Thompson AJ. Strategies for optimizing MRI techniques aimed at monitoring disease activity in multiple sclerosis treatment trials. *Journal of Neurology* 1997; **244**: 76–84.
70. Filippi M, Horsfield MA, Ader HJ, *et al.* Guidelines for using quantitative measures of brain magnetic resonance imaging abnormalities in monitoring the treatment of multiple sclerosis. *Annals of Neurology* 1998; **43**: 499–506.
71. IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta 1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. *Neurology* 1995; **45**: 1277–1285.
72. Thompson AJ, Kermode AG, MacManus DG, *et al.* Patterns of disease activity in multiple sclerosis: clinical and magnetic resonance imaging study. *British Medical Journal* 1990; **300**: 631–634.
73. Filippi M, Campi A, Mammi S, *et al.* Brain magnetic resonance imaging and multimodal evoked potentials in benign and secondary progressive multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry* 1995; **58**: 31–37.
74. Filippi M, Paty DW, Kappos L, *et al.* Correlations between changes in disability and T2-weighted brain MRI activity in multiple sclerosis. *Neurology* 1995; **45**: 255–260.
75. Gasperini C, Horsfield MA, Thorpe JW, *et al.* Macroscopic and microscopic assessment of disease burden by MRI in multiple sclerosis: relationship to clinical parameters. *Journal of Magnetic Resonance Imaging* 1996; **6**: 580–584.
76. Miller DH, Grossman RI, Reingold SC, McFarland HF. The role of magnetic resonance techniques in understanding and managing multiple sclerosis. *Brain* 1998; **121**: 3–24.
77. Kappos L, Moeri D, Radue EW, *et al.* Predictive value of gadolinium-enhanced MRI for relapse rate and changes in disability/impairment in multiple sclerosis: a metaanalysis. *The Lancet* 1999; **353**: 964–969.
78. Filippi M, Grossman RI. MRI techniques to monitor MS evolution. The present and the future. *Neurology* 2002; **58**: 1147–1153.
79. Li DKB, Filippi M, Petkau J, Held U, Daumer M. T2 lesion burden on MRI plateaus as MS disability accumulates. *Multiple Sclerosis* 2003; **9**: S58.
80. Miller DH, Rudge P, Johnson J, *et al.* Serial gadolinium-enhanced magnetic resonance imaging in multiple sclerosis. *Brain* 1988; **111**: 927–939.
81. Tortorella C, Rocca MA, Codella C, *et al.* Disease activity in multiple sclerosis studied with weekly triple dose magnetic resonance imaging. *Journal of Neurology* 1999; **246**: 689–692.
82. Kermode AG, Thompson AJ, Tofts P, *et al.* Breakdown of the blood brain barrier precedes symptoms and other MRI signs of new lesion in multiple sclerosis: pathogenetic and clinical implication. *Brain* 1990; **113**: 1477–1489.
83. Thompson AJ, Miller DH, Youl BD, *et al.* Serial gadolinium-enhanced MRI in relapsing/remitting multiple sclerosis of varying disease duration. *Neurology* 1992; **42**: 60–63.
84. Thompson AJ, Kermode AG, Wicks D, *et al.* Major differences in the dynamics of primary and secondary progressive multiple sclerosis. *Annals of Neurology* 1991; **29**: 53–62.
85. Filippi M, Rossi P, Colombo B, Pereira C, Comi G. Serial contrast-enhanced MR in patients with multiple sclerosis and varying levels of disability. *American Journal of Neuroradiology* 1997; **18**: 1549–1556.
86. Koudriavtseva T, Thompson AJ, Fiorelli M, *et al.* Gadolinium enhanced MRI disease activity in relapsing/remitting multiple sclerosis. *Journal of Neurology Neurosurgery and Psychiatry* 1997; **62**: 285–287.
87. Molyneux PD, Filippi M, Barkhof F, *et al.* Correlations between monthly enhanced MRI lesion rate and changes in T2 lesion volume in multiple sclerosis. *Annals of Neurology* 1998; **43**: 332–339.
88. Simon JH. From enhancing lesions to brain atrophy in MS. *Journal of Neuroimmunology* 1999; **98**: 7–151.
89. Zivadinov R, Zorzon M. Is gadolinium enhancement predictive of the development of brain atrophy in multiple sclerosis? A review of literature. *Journal of Neuroimaging* 2002; **12**: 302–309.

90. Stone LA, Smith E, Albert PS, *et al.* Blood-brain barrier disruption on contrast enhanced MRI in patients with mild relapsing-remitting multiple sclerosis: relationship to course, gender and age. *Neurology* 1995; **45**: 1122–1126.
91. Losseff N, Kingsley D, McDonald WI, Miller DH, Thompson AJ. Clinical and magnetic resonance imaging predictors in primary and secondary progressive MS. *Multiple Sclerosis* 1996; **1**: 218–222.
92. Filippi M, Rocca MA. MRI aspects of the “inflammatory phase” of multiple sclerosis. *Neurological Sciences* 2003; **24**: S275–278.
93. Fazekas F, Barkhof F, Filippi M, *et al.* The contribution of magnetic resonance imaging to the diagnosis of multiple sclerosis. *Neurology* 1999; **53**: 448–456.
94. Simon JH, Jacobs LD, Campion M, *et al.* Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. *Annals of Neurology* 1998; **43**: 79–87.
95. Sorensen PS, Wanscher B, Jensen CV, *et al.* Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. *Neurology* 1998; **50**: 1273–1281.
96. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging – measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. *Annals of Neurology* 2001; **49**: 290–297.
97. Miller DH, Khan OA, Sheremata WA, *et al.* A controlled trial of natalizumab for relapsing multiple sclerosis. *New England Journal of Medicine* 2003; **348**: 15–23.
98. Metz LM, Zhang Y, Yeung M, *et al.* Minocycline reduces gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. *Annals of Neurology* 2004; **55**: 756.
99. Rizvi SA, Agius MA. Current approved options for treating patients with multiple sclerosis. *Neurology* 2004; **63**: S8–S14.
100. Rose JW, Watt HE, White AT, Carlson NG. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. *Annals of Neurology* 2004; **56**: 864–867.
101. Vollmer T, Key L, Durkalski V, *et al.* Oral simvastatin treatment in relapsing-remitting multiple sclerosis. *The Lancet* 2004; **363**: 1607–1608.
102. Miller DH, Molyneux PD, Barker GJ, MacManus DG, Moseley IF, Wagner K. Effect of interferon-beta1b on magnetic resonance imaging outcomes in secondary progressive multiple sclerosis: results of a European multicenter, randomized, double-blind, placebo-controlled trial. European Study Group on Interferon-beta1b in secondary progressive multiple sclerosis. *Annals of Neurology* 1999; **46**: 850–859.
103. Paolillo A, Coles AJ, Molyneux PD, *et al.* Quantitative MRI in patients with secondary progressive MS treated with monoclonal antibody Campath 1H. *Neurology* 1999; **53**: 751–757.
104. Rice GPA, Filippi M, Comi G. Cladribine and progressive MS. Clinical and MRI outcomes of a multicenter controlled trial. *Neurology* 2000; **54**: 1145–1155.
105. The North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology* 2004; **63**: 1788–1795.
106. Li D, Abdalla JA. Long-term observational follow-up of the PRISMS cohort: analyses of MRI BOD shows benefit of high dose, high frequency IFN beta-1^o (Rebif). *Neurology* 2004; **62**: A153–A154.
107. Coles A, Deans J, Compston A. Campath-1H treatment of multiple sclerosis: lessons from the bedside for the bench. *Clinical Neurology and Neurosurgery* 2004; **106**: 270–274.
108. Giugni E, Paolillo A, Tomassini V, *et al.* An active scan at 12th month of therapy is associated with a worse response to IFN beta over the subsequent five years of treatment in RRMS. *Neurology* 2003; **60**: A251–A252.
109. Rudick RA, Lee JC, Simon J, Ransohoff RM, Fisher E. Defining interferon beta response status in multiple sclerosis patients. *Annals of Neurology* 2004; **56**: 548–555.
110. Lycklama à Nijeholt GJ, van Walderveen MAA, van Waesberghe JH, *et al.* Brain and spinal cord abnormalities in multiple sclerosis. Correlation between MRI parameters, clinical subtypes and symptoms. *Brain* 1998; **121**: 687–697.
111. Stevenson VL, Miller DH, Rovaris M, *et al.* Primary and transitional progressive MS, a clinical and MRI cross-sectional study. *Neurology* 1999; **52**: 839–845.
112. van Walderveen MA, Truyen L, van Osten BW, *et al.* Development of hypointense lesion on T1-weighted spin echo magnetic resonance images in multiple sclerosis: relation to inflammatory activity. *Archives of Neurology* 1999; **56**: 345–351.
113. van Walderveen MAA, Lycklama à Nijeholt GJ, Adèr HJ, *et al.* Hypointense lesions on T1 weighted SE MRI: relation to clinical characteristic in subgroups of multiple sclerosis patients. *Archives of Neurology* 2001; **58**: 76–81.
114. Truyen L, van Waesberghe JHTM, van Walderveen MAA, *et al.* Accumulation of hypointense lesions (black holes) on T1 spin-echo MRI correlates with disease progression in multiple sclerosis. *Neurology* 1996; **47**: 1469–1476.
115. Iannucci G, Minicucci L, Rodegher M, Sormani MP, Comi G, Filippi M. Correlations between clinical and MRI involvement in multiple sclerosis: assessment using T1, T2 and MT histograms. *Journal of Neurology* 1999; **171**: 121–129.
116. van Walderveen MAA, Barkhof F, Hommes OR, *et al.* Correlating MRI and clinical activity in multiple sclerosis: relevance of hypointense lesions on short TR/short TE (T1-weighted) spin-echo images. *Neurology* 1995; **45**: 1684–1690.
117. Losseff NA, Wang L, Lai HM, *et al.* Progressive cerebral atrophy in multiple sclerosis: a serial MRI study. *Brain* 1996; **119**: 2009–2019.
118. Simon JH, Lull J, Jacobs LD, *et al.* A longitudinal study of T1 hypointense lesions in relapsing MS: MSCRG trial of interferon beta-1a. *Neurology* 2000; **55**: 185–192.
119. Barkhof F, van Waesberghe JH, Filippi M, *et al.* T1 hypointense lesions in secondary progressive multiple sclerosis: effect of interferon beta-1b treatment. *Brain* 2001; **124**: 1396–1402.
120. Filippi M, Rovaris M, Rice GPA, *et al.* The effect of Cladribine on T1 ‘black hole’ changes in progressive MS. *Journal of the Neurological Sciences* 2000; **176**: 42–44.
121. Patti F, Amato MP, Filippi M, Gallo P, Trojano M, Comi G. A double blind, placebo-controlled, phase II,

- add-on study of cyclophosphamide (CTX) for 24 months in patients affected by multiple sclerosis on a background therapy with interferon-beta study denomination: CY-CLIN. *Journal of the Neurological Sciences* 2004; **223**: 69–71.
122. Brex PA, Molyneux PD, Smiddy P, *et al.* The effect of IFN β -1b on the evolution of enhancing lesions in secondary progressive MS. *Neurology* 2001; **57**: 2185–2190.
 123. Filippi M, Rovaris M, Rocca MA, Sormani MP, Wolinsky JS, Comi G for the European/Canadian Glatiramer Acetate Study Group. Glatiramer acetate reduces the proportion of new MS lesions evolving into “black holes”. *Neurology* 2001; **57**: 731–733.
 124. Dalton CM, Miszkiet KA, Barker GJ, *et al.* Effect of natalizumab on conversion of gadolinium enhancing lesions to T1 hypointense lesions in relapsing multiple sclerosis. *Journal of Neurology* 2004; **251**: 407–413.
 125. Benedict RH, Carone DA, Bakshi R. Correlating brain atrophy with cognitive dysfunction, mood disturbances, and personality disorder in multiple sclerosis. *Journal of Neuroimaging* 2004; **14**: 36S–45S.
 126. Zivadinov R, Bakshi R. Central nervous system atrophy and clinical status in multiple sclerosis. *Journal of Neuroimaging* 2004; **14**: 27S–35S.
 127. Hohol MJ, Guttmann CR, Orav J, *et al.* Serial neuropsychological assessment and magnetic resonance imaging analysis in multiple sclerosis. *Archives of Neurology* 1997; **54**: 1018–1025.
 128. Fisher E, Rudick RA, Simon JH, *et al.* Eight-year follow-up study of brain atrophy in patients with MS. *Neurology* 2002; **59**: 1412–1420.
 129. Filippi M, Colombo B, Rovaris M, Pereira C, Martinelli V, Comi G. A longitudinal magnetic resonance imaging study of the cervical cord in multiple sclerosis. *Journal of Neuroimaging* 1997; **7**: 78–80.
 130. Chard DT, Griffin CM, Parker GJ, Kapoor R, Thompson AJ, Miller DH. Brain atrophy in clinically early relapsing–remitting multiple sclerosis. *Brain* 2002; **125**: 327–337.
 131. De Stefano N, Matthews PM, Filippi M, *et al.* Evidence of early cortical atrophy in MS: relevance of white matter changes and disability. *Neurology* 2003; **60**: 1157–1162.
 132. Pagani E, Rocca MA, Gallo A, *et al.* Regional brain atrophy evolves differently in patients with multiple sclerosis according to clinical phenotype. *American Journal of Neuroradiology* 2005; **26**: 341–346.
 133. Bermel R, Bakshi R, Tjoa C, Puli S, Jacobs L. Bicaudate ratio as an MRI marker of brain atrophy in multiple sclerosis. *Archives of Neurology* 2002; **59**: 275–280.
 134. Benedict RHB, Zivadinov R, Carone DA, *et al.* Regional lobar atrophy predicts memory impairment in multiple sclerosis. *American Journal of Neuroradiology* 2005; **26**: 1824–1831.
 135. Rudick RA, Fisher E, Lee JC, Simon J, Jacobs L. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing–remitting MS. Multiple Sclerosis Collaborative Research Group. *Neurology* 1999; **53**: 1698–1704.
 136. Filippi M, Rovaris M, Iannucci G, Mennea S, Sormani MP, Comi G. Whole brain volume changes in patients with progressive MS treated with cladribine. *Neurology* 2000; **55**: 1714–1718.
 137. Molyneux PD, Kappos L, Polman C, *et al.* The effect of interferon beta-1b treatment on MRI measures of cerebral atrophy in secondary progressive multiple sclerosis. *Brain* 2000; **123**: 2256–2263.
 138. Rovaris M, Comi G, Rocca MA, Wolinsky JS, Filippi M and the European/Canadian Glatiramer Acetate Study Group. Short-term brain volume change in relapsing–remitting multiple sclerosis: effect of glatiramer acetate and implications. *Brain* 2001; **124**: 1803–1812.
 139. Smith D. Preliminary analysis of a trial of pulse cyclophosphamide in OFN-beta-resistant active MS. *Journal of the Neurological Sciences* 2004; **223**: 73–79.
 140. Sormani MP, Rovaris M, Valsasina P, Wolinsky JS, Comi G, Filippi M. Measurement error of two different techniques for brain atrophy assessment in multiple sclerosis. *Neurology* 2004; **62**: 1432–1434.
 141. Pelletier D, Garrison K, Henry R. Measurement of whole-brain atrophy in multiple sclerosis. *Journal of Neuroimaging* 2004; **14**: 11S–19S.
 142. Rovaris M, Agosta F, Sormani MP, *et al.* Conventional and magnetization transfer MRI predictors of clinical multiple sclerosis evolution: a medium-term follow-up study. *Brain* 2003; **126**: 2323–2332.
 143. Richert ND, Ostuni JL, Bash CN, Duyn JH, McFarland HF, Frank JA. Serial whole-brain magnetization transfer imaging in patients with relapsing–remitting multiple sclerosis at baseline and during treatment with interferon beta-1b. *American Journal of Neuroradiology* 1998; **19**: 1705–1713.
 144. Richert ND, Ostuni JL, Bash CN, Leist TP, McFarland HF, Frank JA. Interferon beta-1b and intravenous methylprednisolone promote lesion recovery in multiple sclerosis. *Multiple Sclerosis* 2001; **7**: 49–58.
 145. Kita M, Goodkin DE, Bacchetti P, Waubant E, Nelson SJ, Majumdar S. Magnetization transfer ratio in new MS lesions before and during therapy with IFN β -1a. *Neurology* 2000; **54**: 1741–1745.
 146. Inglese M, van Waesberghe JH, Rovaris M, *et al.* The effect of interferon beta-1b on quantities derived from MT MRI in secondary progressive MS. *Neurology* 2003; **60**: 853–860.
 147. Filippi M, Rocca MA, Pagani E, *et al.* European study on intravenous immunoglobulin in multiple sclerosis: results of magnetization transfer magnetic resonance imaging analysis. *Archives of Neurology* 2004; **61**: 1409–1412.
 148. Horsfield MA, Barker GJ, Barkhof F, Miller DH, Thompson AJ, Filippi M. Guidelines for using quantitative magnetization transfer magnetic resonance imaging for monitoring treatment of multiple sclerosis. *Journal of Magnetic Resonance Imaging* 2003; **17**: 389–3897.
 149. Ropele S, Filippi M, Valsasina P, *et al.* Assessment and correction of B1-induced errors in magnetization transfer ratio measurements. *Magnetic Resonance in Medicine* 2005; **53**: 134–140.
 150. Gonen O, Catalaa I, Babb JS, *et al.* Total brain N-acetylaspartate: a new measure of disease load in MS. *Neurology* 2000; **54**: 15–19.
 151. Sarchielli P, Presciutti O, Tarducci R, *et al.* 1H-MRS in patients with multiple sclerosis undergoing treatment with interferon beta-1a: results of a preliminary study. *Journal of Neurology, Neurosurgery, and Psychiatry* 1998; **64**: 204–212.
 152. Narayanan S, De Stefano N, Francis GS, *et al.* Axonal metabolic recovery in multiple sclerosis patients treated

- with interferon beta-1b. *Journal of Neurology* 2001; **248**: 979–986.
153. Schubert F, Seifert F, Elster C, *et al.* Serial 1H-MRS in relapsing-remitting multiple sclerosis: effects of interferon-beta therapy on absolute metabolite concentrations. *MAGMA* 2002; **14**: 213–222.
154. Parry A, Corkill R, Blamire AM, *et al.* Beta-interferon treatment does not always slow the progression of axonal injury in multiple sclerosis. *Journal of Neurology* 2003; **250**: 171–178.
155. Khan O, Shen Y, Ching W, *et al.* Combining immunomodulation and neuroprotection: cerebral axonal recovery in relapsing-remitting multiple sclerosis patients treated with glatiramer acetate. *Multiple Sclerosis* 2003; **9**(Suppl. 1): 63
156. Narayana PA, Wolinsky JS, Rao SB, He R, Mehta M.; PROMiSe Trial MRSI Group. Multicentre proton magnetic resonance spectroscopy imaging of primary progressive multiple sclerosis. *Multiple Sclerosis* 2004; **10**: S73–S78.