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Evolving role of MRI in optimizing the treatment of multiple sclerosis: Canadian Consensus recommendations

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Abstract

Background: Magnetic resonance imaging (MRI) is increasingly important for the early detection of suboptimal responders to disease-modifying therapy for relapsing–remitting multiple sclerosis. Treatment response criteria are becoming more stringent with the use of composite measures, such as no evidence of disease activity (NEDA), which combines clinical and radiological measures, and NEDA-4, which includes the evaluation of brain atrophy.

Methods: The Canadian MRI Working Group of neurologists and radiologists convened to discuss the use of brain and spinal cord imaging in the assessment of relapsing–remitting multiple sclerosis patients during the treatment course.

Results: Nine key recommendations were developed based on published sources and expert opinion. Recommendations addressed image acquisition, use of gadolinium, MRI requisitioning by clinicians, and reporting of lesions and brain atrophy by radiologists. Routine MRI follow-ups are recommended beginning at three to six months after treatment initiation, at six to 12 months after the reference scan, and annually thereafter. The interval between scans may be altered according to clinical circumstances.

Conclusions: The Canadian recommendations update the 2006 Consortium of MS Centers Consensus revised guidelines to assist physicians in their management of MS patients and to aid in treatment decision making.

***Keywords*:** Multiple sclerosis, magnetic resonance imaging, MRI, recommendations, treatment response

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Introduction

Multiple sclerosis (MS) is a chronic disorder of the central nervous system (CNS) in which activation of autoaggressive immune cells results in focal and diffuse inflammation, demyelination and axonal and neuronal loss. Conventional magnetic resonance imaging (MRI) is highly sensitive in detecting white-matter focal inflammatory activity, as shown by gadolinium (Gd)-enhancing T1-weighted lesions or new T2-weighted lesions. MRI changes are routinely used as endpoints in phase II and III studies of disease-modifying therapies (DMTs). MRI measures, such as a reduction in Gd-enhancing T1 or new/enlarging T2 lesion formation, are useful surrogates of relapse reduction and allow clinical trials to have smaller sample sizes and be of shorter duration.

In clinical practice, MRI has assumed an increasingly important role following the incorporation of imaging findings into the diagnostic criteria developed by the International Panel on the Diagnosis of Multiple Sclerosis (the ''McDonald criteria'').[1]

In clinically isolated syndrome (CIS), T2 lesion load is prognostic of conversion to clinically definite MS and greater long-term disability as assessed by the Expanded Disability Status Scale (EDSS).[2] Gd-enhancing T1 lesion number is associated with greater

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brain atrophy,[3] which in turn is prognostic of disability progression.[4] The correlation between T2 lesion volume and EDSS score change appears to be strongest in the first five years after diagnosis.[5] In untreated relapsing–remitting MS (RRMS) patients, the number of new/enlarging T2 lesions or the number of Gd-enhancing T1 lesions is weakly correlated with accumulation of disability over the short term,[6] but is more strongly correlated over the long term.[7]

The predictive value of ongoing MRI activity for long-term outcomes is more robust in treated than untreated RRMS patients. Rudick et al. reported that the number of Gd-enhancing lesions in patients on interferon-beta (IFNβ)-1a was a better predictor of EDSS progression than relapses.[8] In the first year of IFNβ treatment, the presence of ≥1 Gd-enhancing T1 or new T2 lesions was associated with a significantly higher risk of relapses and EDSS progression. Prosperini et al. estimated that the risk of EDSS progression was 10-fold higher with one new T2 lesion, 20-fold higher with two new T2 lesions, and 30-fold higher for ≥3 new T2 lesions during the first year of therapy.[9] More recently, a 15-year follow-up of the pivotal trial of intramuscular IFNβ-1a found that in the first two years of treatment, ongoing disease activity was strongly associated with more severe long-term disability, with odds ratios of 8.96 with ≥2 Gd-enhancing lesions, 2.90 with ≥3 new T2 lesions, and 4.44 with relapses.[10] A systematic analysis also found that ongoing disease activity (≥2 new T2 lesions or new Gd-enhancing lesions) in the first six to 24 months of IFNβ treatment was predictive of treatment failure and future disability progression.[11]

Sormani et al. determined that patients with ongoing clinical and radiological disease activity after one year of treatment with subcutaneous IFNβ-1a had a 50% risk of EDSS progression at four-year follow-up.[12] A separate meta-analysis of 40 trials of CIS, RRMS and secondary-progressive MS (SPMS) supported a significant association between T2 lesion measures (lesion number and volume) in the first two years of treatment and disability, as measured by EDSS progression.[13] In contrast to prior studies, this analysis included recent trials of newer agents, such as fingolimod, dimethyl fumarate (DMF), and alemtuzumab, and there was the suggestion that the strength of the association between T2 lesion measures and EDSS score may differ with these agents.[13]

As MRI focal inflammation contributes strongly to relapse and disability, some authors have argued that MRI outcomes are useful biomarkers that can be applied in the appropriate clinical or treatment-specific context.[14] However, MRI may not be optimally employed in routine clinical practice, and recommendations have been slow to adopt the use of periodic MRI scans in the routine evaluation of treatment response. The Consortium of MS Centers did not recommend follow-up MRIs in treated or untreated patients unless clinically indicated.[15] Subsequent recommendations have advocated routine MRI monitoring of treatment effects in clinical trials but not in clinical practice.[16,17]

The use of surveillance MRI for the early detection of treatment non-responders has become more widespread in recent years, in part because of the availability of a broader range of DMTs, which has provided clinicians with more options for optimizing treatment. Recent treatment optimization recommendations now include MRI criteria for evaluating patients' therapeutic response.[18] The role of MRI in evaluating treatment response is, in part, a recognition of the value of documenting subclinical inflammatory disease activity, and perhaps also the accumulation of irreversible CNS damage.[19] This is particularly salient in treated patients. MRI evidence of ongoing focal white-matter inflammation despite a treatment that is intended to suppress inflammation is arguably sufficient to indicate a suboptimal therapeutic response.[18]

The higher standard for therapeutic response is reflected in the emerging use of the composite measure of no evidence of disease activity (NEDA) rather than the Rio criteria. NEDA is generally defined as no relapses, no sustained EDSS progression confirmed at three or six months, and no MRI activity (no Gd-enhancing T1 or new/enlarging T2 lesions). In clinical trials to date, approximately one-third of patients treated with natalizumab, fingolimod or alemtuzumab achieve NEDA in the first two years of therapy.[20–22]

The definition of NEDA is still evolving and it has not been entirely settled whether some components of the composite score (e.g. new T2 vs. Gd+ T1 lesions) have greater predictive value for long-term disability outcomes; there is evidence to suggest that MRI lesions may be more predictive of disability than relapses in patients taking IFNβ.[9] Preliminary efforts have been made to further refine NEDA by including brain volume change (NEDA-4) as a measure of treatment efficacy.[23] Since brain volume loss occurs in healthy individuals, a cut-off value of less than 0.4%/year has been proposed for the ''no atrophy'' criterion of NEDA-4.

As NEDA or other measures of ongoing disease activity are largely determined by MRI activity

rather than clinical measures at the start of treatment,[24] there is a need to standardize the technical specifications of MRI scans and the frequency of their use. Accordingly, a Canadian MRI Consensus Group convened in May 2014 to update recommendations on the standardization of MR image acquisition and MRI requisitioning/reporting in treated RRMS patients in an effort to assist clinicians in their decision making. The group's recommendations were in accordance with published evidence and, where data were lacking, on group consensus based on expert opinion. The group achieved a majority consensus for all recommendations, with some dissenting opinions noted in the text. A complete list of recommendations is provided in Table 1.

Canadian MRI Consensus Group recommendations

Recommendation 1: Routine MRI follow-up of patients after treatment initiation is recommended to identify ongoing inflammatory disease activity

Current DMTs target different aspects of the dysregulated immune response, and their benefit is primarily due to their anti-inflammatory effects. As such, the presence of ongoing inflammation during the treatment course is indicative of a suboptimal treatment response.[18] There is some evidence that ongoing disease activity in the first one to two years of treatment is predictive of poorer outcomes. In accordance with recent recommendations,[18] the presence of two or more lesions (new Gd-enhancing lesions or an accumulation of new T2 lesions per year) may warrant a change in therapy. Newer therapies can produce a significantly greater reduction in some markers of disease activity, as shown by phase III studies of fingolimod versus intramuscular IFNβ-1a,[25] DMF versus glatiramer acetate (post-hoc analysis),[26] and alemtuzumab versus subcutaneous IFNβ-1a.[27] The long-term benefits of switching treatments have not been determined. Routine surveillance MRI may be useful, most notably in the first few years of treatment, to allow for earlier identification of ongoing disease activity and to employ another treatment when it will be most effective. The timing of scans is addressed in Recommendation 3.

Recommendation 2: A reference MRI is recommended at six months after treatment initiation

A reference scan is recommended to provide a baseline assessment of T2 lesions, with which the follow-up scan can be compared for assessment of disease activity in treated patients. Ideally, the reference scan should be obtained sufficiently long after a treatment is initiated for it to have become effective (usually three to six months). This provides the clinician with greater certainty that new T2 lesions on subsequent scans represent disease activity that is occurring despite treatment.

Since access to MRI may be limited in some centers, it may be difficult to obtain a scan at the most opportune time. If the reference scan can only be obtained before a treatment is fully effective, evidence of some ongoing activity should not be interpreted as a suboptimal response. Rather, new T2 lesions on follow-up scans will need to be interpreted in the context of the level of disease activity at the time treatment was initiated, and the time required for the new therapy to become effective. The presence of T1-gadolinium activity on the follow-up scans may be particularly helpful in this circumstance. Since the duration of enhancement is brief (about three to 12 weeks depending on the protocol use[28]), Gd-enhancing lesions indicate recent activity after a drug has had time to become effective, whereas T2 counts may include lesions that occurred prior to the onset of drug effect.

Recommendation 3: The first follow-up scan should be obtained at six to 12 months after the reference scan

Following the on-treatment reference scan, the first follow-up scan is recommended at six to 12 months. More frequent scans may be obtained if clinically indicated. MRI should be delayed one month in patients receiving a course of intravenous steroids. A follow-up scan at three months postpartum may be advised in women who have discontinued treatment owing to pregnancy or breastfeeding; the presence of significant disease activity may influence the choice of therapy when treatment is restarted. A longer interval between scans (e.g. every 24 months) may be considered for patients with no disease activity on the previous two or three scans.

Recommendation 4: T1-weighted scans with gadolinium are recommended for the reference and first follow-up scan

Gd enhancement indicates active inflammation at the time of the scan, whereas new T2 lesions integrate activity that has occurred in the interval between the scans being compared. If feasible, Gd is preferred for the first on-treatment scan to demonstrate ongoing focal inflammatory activity despite treatment. Once an on-treatment reference scan is available, the clinician will be able to use new T2 lesions with respect to the previous on-treatment scan to identify ongoing focal inflammatory activity, so that gadolinium will be less necessary. Gd-enhanced scans are also

Table 1. Summary of recommendations on the use of magnetic resonance imaging (MRI) in relapsing–remitting patients during treatment with a disease-modifying therapy.

	Recommendation	Comment
1	Routine MRI follow-up of patients after treatment initiation is recommended to identify ongoing inflammatory disease activity.	Ongoing disease activity in the first one to two years of treatment is predictive of poorer outcomes. A change in therapy may be warranted if there is evidence of ongoing disease activity.
2	A reference MRI is preferably obtained after the therapy has had time to become effective (usually ~3–6 months after treatment initiation; less for natalizumab; more for glatiramer acetate).	If access to MRI is limited and it is not feasible to obtain an early reference scan, interpretation of new T2 lesions with respect to a pre-treatment reference scan must take into consideration that any new lesions may have formed before there was enough time for the treatment to be fully effective.
3	The first follow-up scan should be obtained at six to 12 months after the reference scan and annually thereafter.	More frequent scans may be advisable if clinically indicated. A longer interval between scans may be considered if no disease activity has been present on the previous two or three scans.
4	T1-weighted scans with gadolinium are recommended for the first follow-up scan, if a post-treatment reference scan is not available.	Gadolinium is recommended to demonstrate ongoing inflammatory activity and avoid ambiguity about when any new T2 lesions may have formed with respect to treatment onset. T2 lesions that are enhancing should be counted only once as unique active lesions.
5	The recommended brain MRI sequences: - Sagittal FLAIR - Axial FLAIR - Axial T2 - Post-Gd T1 (3D FLAIR may replace sagittal/axial FLAIR, if available)	Gadolinium: single dose (0.1 mmol/kg) administered over 30 seconds. Post-gadolinium T1 obtained after a minimum interval of five minutes.
6	Minimum MRI scanner field strength of 1.5T. Slice thickness: ≤ 3 mm (min. standard ≤ 5 mm) with no gap.	Use subcallosal line as the reference plane of acquisition for sagittal FLAIR. Include the cervical spine to the extent feasible.
7	Separate imaging of the spinal cord is not recommended in routine practice. If clinically indicated, the recommended spinal cord sequences: - Sagittal T2 - Sagittal T1 - Sagittal PD or STIR - Axial T2. Slice thickness: ≤ 3 mm (sagittal), or ≤ 4 mm (axial), with no gap.	Sagittal FLAIR that includes the cervical spine is generally sufficient. No additional gadolinium is required if the spinal cord study immediately follows gadolinium administration for brain imaging.
8	The information provided by clinicians requisitioning an MRI should be sufficient to allow the radiologist to address the clinical issue.	Requisitions to include: a) Reason for scan. b) Patient information. c) Disease-modifying therapy. d) Other medications. e) Date/location of prior MRIs.

(continued)

Table 1. Continued.

	Recommendation	Comment
9	The information provided by the radiologist in the MRI report should be sufficient to assist in the treating physician's clinical decision making.	Reports to include: a) Date of scan. b) Gadolinium use. c) Comparison with previous scan. d) Evidence of new disease activity. e) Number of new lesions (T2/T1). f) Lesion size. g) Overall assessment, including presence (definite/probable) and extent (number of new/enlarging lesions or gadolinium-enhancing lesions) of disease activity; change in T2 lesion volume; and evidence of brain atrophy.

FLAIR: fluid-attenuated inversion recovery; STIR: short tau inversion recovery; PD: proton density; MRI: magnetic resonance imaging; 3D: three-dimensional.

preferred since they are less subject to the technique used to obtain the MRI and there are fewer uncertainties in the comparison of paired scans. Identifying new T2 lesions can be challenging, most notably if lesions are small, or images were obtained using a different acquisition technique or a different scanner. Methods that can provide more reliable image analysis are needed.

Rigorous review by an individual experienced in the assessment of MS is required. In determining lesion count, it should be noted that T2 lesions that are enhancing on the same scan should be counted only once as unique active lesions. This recommendation is in accordance with the Consortium of MS Clinics (CMSC) revised guidelines.[15]

While Gd-enhanced scans are preferred, there may be barriers to use at some centers, such as limited access to Gd, the cost of the contrast agent, and the difficulties in scheduling because of the need to obtain these scans during hours when there is medical supervision, in case of rare contrast reactions.

Recommendation 5: A standardized MRI protocol is important during patient follow-up. The recommended brain MRI sequences are sagittal fluid-attenuated inversion recovery (FLAIR), axial FLAIR, axial T2 and post-Gd T1. Axial proton density (PD) and T2 may be acquired as a dual echo

The addition of diffusion-weighted imaging is recommended for follow-up scans since it may be useful to exclude MS mimics, provide additional information about lesion severity and to assist in the early identification of progressive multifocal leukoencephalopathy (PML).

A single dose of Gd (0.1 mmol/kg) administered over 30 seconds is recommended. Post-Gd T1 should be obtained after a minimum five-minute delay. Other sequences may be acquired during this period. In contrast to other recommendations,[15] pre-Gd axial T1 is considered optional, although it was noted that pre-Gd T1 is useful to ensure that what is seen is definitely enhancement. If pre-Gd T1 is obtained, gadolinium should be administered immediately afterward, followed by sagittal and axial FLAIR, axial T2, and post-Gd T1. This recommendation follows the CMSC guidelines.[15] Three-dimensional (3D) FLAIR may replace sagittal/axial FLAIR, if available.

Recommendation 6: Whole-brain imaging using an MRI scanner with a minimum field strength of 1.5T is recommended

For all axial sequences, the subcallosal line should be used as the reference plane of acquisition to allow for consistent comparisons with follow-up scans, as recommended by the CMSC guidelines.[15] The recommended slice thickness is ≤ 3 mm with no gap; if this cannot be achieved, the minimum acceptable standard is ≤ 5 mm with no gap.

Recommendation 7: Separate imaging of the spinal cord is not recommended in routine practice

Routine follow-up spinal cord studies have not been generally helpful. If clinically indicated, the recommended spinal cord sequences are sagittal T2, sagittal T1, sagittal PD or short tau inversion recovery (STIR) or phase-sensitive inversion recovery (PSIR), and axial T2, in accordance with CMSC guidelines.[15] The recommended slice thickness is ≤ 3 mm (sagittal), or ≤ 4 mm (axial), with no gap.

No additional Gd is required if the spinal cord study immediately follows Gd administration for brain imaging.

Recommendation 8: The information provided by clinicians requisitioning an MRI should be sufficient to allow the radiologist to address the clinical issue

The following information should be provided by the referring physician on the MRI requisition:

a. Reason for scan (i.e. diagnosis, follow-up of diagnosed MS patient). If an initial post-treatment scan, the requirement for Gd to establish a new reference baseline should be stated. It should also be specified if the baseline on-treatment scan has been performed and that the current scan (with or without Gd) is a follow-up to monitor treatment response.
b. Patient information. This includes age, date of MS diagnosis or first symptoms, present clinical disease activity, comorbidities, allergies, and other relevant information.
c. DMT. This should include the current DMT and duration on treatment.
d. Date/location of prior MRIs to be used as comparator scans.

Recommendation 9: The information provided by the radiologist in the MRI report should be sufficient to assist in the treating physician's clinical decision making

The following information should be provided by the radiologist in the MRI report:

a. Date of scan.
b. Gd use (yes/no).
c. Comparison with previous scan. This should include the date of the prior scan and a technical summary of comparability.
d. Evidence of new disease activity (Gd-enhancing T1 or new/enlarging T2). Evidence of activity should be classified as definite/probable/no.
e. Number of new lesions (T2/T1). The number may be specified approximately, or as >10 when counts are high. Individual active lesions must be counted only once.
f. Lesion size. The radiologist may comment on the size of new lesions to support certainty. Lesion location (e.g. supratentorial, infratentorial) may be indicated if it appears to be clinically relevant.
g. The radiologist's overall assessment, to assist the clinician in evaluating the relevance of MRI findings with respect to lesion activity and possible complications of therapy (e.g. PML). The assessment may include a discussion of the presence (definite/probable) and extent (number of new/enlarging lesions or Gd-enhancing lesions) of disease activity. In comparing scans, the radiologist may note if there is a change in T2 lesion volume and diffuse/confluent high T2 changes, and should comment on whether there is evidence of significant brain atrophy. The reporting of brain atrophy will usually be confined to two scans obtained at least one year apart.

Assessment of brain atrophy

It is now recognized that conventional MR imaging of focal inflammatory lesions only partially captures the histopathological changes that occur in MS. Also important is the extent of diffuse inflammation in the whole brain and meninges that results in axonal injury, cortical demyelination and tissue loss in normal-appearing white matter (NAWM) and gray matter (NAGM).[29] Long-term follow-up studies have shown that early brain volume loss, most notably GM atrophy, is significantly correlated with disability progression,[30] and a method for categorizing MRI phenotypes based on lesion volume and atrophy has recently been proposed.[31] Brain volume change can be detected over a six-month period in groups of patients, and is now routinely used in phase III testing. However, reliable detection of atrophy in individual patients will take longer (>1 year), except in severe cases. In the evaluation of treatment non-response, the sensitivity of clinical and radiological assessments has been shown to be significantly improved with the addition of brain atrophy.[32] At one year, relapses + EDSS progression + new active lesions + brain volume change (hazard ratio (HR) 14.4) was more useful in predicting treatment failure than relapses + EDSS progression (HR 4.6) or relapses + EDSS progression + new active lesions (HR 10.1).

Longitudinal assessment of brain atrophy is not routinely performed in practice, in part because of concerns about biological factors that may confound the analysis (e.g. hydration status and inflammation-related volume changes), as well as the lack of a standardized method for image acquisition, which is required to make this determination. However, the field is evolving rapidly and preliminary recommendations for the assessment and analysis of brain atrophy have been developed.[33] These include the use of volumetric 3D MR acquisition with T1 rather than T2 weighting, and improved automated image segmentation to help in distinguishing WM lesions from GM. Currently, a number of automated methods may be used to evaluate whole-brain

volume change (e.g. structural image evaluation, using normalization, of atrophy (SIENA), Jacobian integration). The optimal approach to determining intra-individual changes in brain volume needs to be determined.

At present, the qualitative reporting of brain volume changes is recommended as part of the routine MRI assessment, as noted in Recommendation 9. Greater effort is needed to have quantitative brain volume measurements made available routinely as part of clinical practice.

Discussion

Two decades ago, radiological assessment of MS was considered to be of secondary importance to clinical measures, and MRI data were not routinely included in pivotal trials of DMTs. Since that time, MRI technology has greatly improved our understanding of the pathogenesis and clinical course of MS, and has been shown to be highly relevant to prognosis and in the assessment of treatment response. Novel imaging techniques, such as magnetization transfer (MT), diffusion tensor imaging (DTI), and MR spectroscopy, have also provided important insights on histopathology, lesion evolution and the extent of tissue damage that occurs throughout the disease course. Indeed, imaging techniques have changed the view of MS as a primarily focal inflammatory disease by characterizing the extensive changes that occur in NAWM and NAGM, which has further informed our understanding of the role of innate immune dysregulation in MS.[34,35]

The role of MRI in the diagnosis and management of MS is rapidly evolving, and will expand as research techniques and technological improvements become more widespread. The use of higher field strengths, such as 3T or 7T, will provide greater sensitivity in detecting WM and GM lesions. An area of increasing importance is GM atrophy, which appears to be a stronger correlate of physical and cognitive disability progression than WM pathology.[36]

As part of the evolution of MRI, the present recommendations support the routine evaluation of radiological response in DMT-treated patients. While this may have had questionable value when treatment options were limited, there is now a broad range of DMTs available and clinicians have the opportunity to modify their treatment plan in patients with a suboptimal response. As the time window for altering the disease course with treatment appears limited, frequent MRIs, at least in the first few years of treatment, are needed to enable more prompt and informed decision making and to improve long-term clinical outcomes in MS patients.

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Conflicts of interest

Dr Arnold reports grants from the Multiple Sclerosis Society of Canada during the conducting of the study; and personal fees from Acorda, Biogen Idec, Genzyne, Roche, Innate Immunotherapeutics, MedImmune, Mitsubishi Pharma, Novartis, Receptos, Sanofi Aventis, Teva and Xenoport outside the submitted work. Dr Li has received research funding from the Canadian Institutes of Health Research and Multiple Sclerosis Society of Canada; acted as a consultant to Vertex Pharmaceuticals; served on the Data and Safety Advisory Board for Opexa Therapeutics; and served on scientific advisory boards for Novartis, Nuron and Roche. He is the director of the UBC MS/MRI Research Group, which has been contracted, in the past five years, to perform central analysis of MRI scans for therapeutic trials with Genzyme, Roche, Merck-Serono, Nuron, Perceptives and Sanofi-Aventis. Dr Hohol has received honoraria for speaking, consulting, and/or advisory board participation from Bayer HealthCare, Biogen Idec, EMD Serono, Genzyme, Novartis, Roche and Teva Neuroscience. Dr Chakraborty has received research grants from GE and Bayer Inc and honoraria from Novartis, but does not have any other direct or indirect conflict of interest regarding the subject matter of this manuscript. Dr Chankowsky has nothing to declare. Dr Alikhani has served on advisory boards for Novartis and Biogen Idec, and has been provided travel support by Novartis and Biogen Idec. Dr. Duquette has received honoraria for speaking, consulting, and advisory board participation; support to attend meetings from Bayer HealthCare, Biogen Idec, EMD Serono, Genzyme, Novartis, Roche and

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