Spinal Cord as an Adjunct to Brain Magnetic Resonance Imaging in Defining "No Evidence of Disease Activity" in Multiple Sclerosis

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CME/CNE Information

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Learning Objectives:
1) Describe the concept of "no evidence of disease activity" in MS.
2) Recognize the role of spinal cord imaging in routine monitoring of MS disease activity.

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Background: *Monitoring patients with multiple sclerosis (MS) for "no evidence of disease activity" (NEDA) may help guide disease-modifying therapy (DMT) management decisions. Whereas surveillance brain magnetic resonance imaging (MRI) is common, the role of spinal cord monitoring for NEDA is unknown.*

Objective: *To evaluate the role of brain and spinal cord 3T MRI in the 1-year evaluation of NEDA.*

Methods: *Of 61 study patients (3 clinically isolated syndrome, 56 relapsing-remitting, 2 secondary progressive), 56 (91.8%) were receiving DMT. The MRI included brain fluid-attenuated inversion recovery and cervical/thoracic T2-weighted fast spin echo images. On MRI, NEDA was defined as the absence of new or enlarging T2 lesions at 1 year.*

Results: *Thirty-nine patients (63.9%) achieved NEDA by brain MRI, only one of whom had spinal cord activity. This translates to a false-positive rate for NEDA based on the brain of 2.6% (95% CI, 0.1%-13.5%). Thirty-eight patients (62.3%) had NEDA by brain and spinal cord MRI. Fifty-five patients (90.2%) had NEDA by spinal cord MRI, 17 of whom had brain activity. Of the 22 patients (36.1%) with brain changes, 5 had spinal cord changes. No evidence of disease activity was sustained in 48.3% of patients at 1 year and was the same with the addition of spinal cord MRI. Patients with MRI activity in either the brain or the spinal cord only were more likely to have activity in the brain (P = .0001).*

Conclusions: *Spinal cord MRI had a low diagnostic yield as an adjunct to brain MRI at 3T in monitoring patients with MS for NEDA over 1 year. Studies with larger data sets are needed to confirm these findings.*
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No evidence of disease activity (NEDA) is a new proposed outcome to monitor the risk of disease progression and the effectiveness of disease-modifying therapy (DMT) in patients with multiple sclerosis (MS). The term *NEDA* is also known as disease activity–free status, freedom from disease activity, and disease-free status.[1-5] This definition typically relies on clinical and cerebral imaging data, namely, the absence of new or enlarging T2 lesions or gadolinium-enhancing lesions and no progression of neurologic disability or clinical relapses.[6]

Magnetic resonance imaging (MRI) plays a critical role in the diagnosis and monitoring of MS.[7,8] The introduction of higher-field (eg, 3T) MRI scanners has shown a higher yield in the detection of MS lesions compared with 1.5T.[9,10] Furthermore, brain MRI at 3T has also provided higher correlations between lesion load and clinical status, including neurologic disability and cognitive function, than at 1.5T.[10] A growing body of evidence has determined that spinal cord MRI involvement shows a particularly close association with MS-related disability.[11-24] In addition, spinal cord involvement manifests early in the disease course; such lesions in presymptomatic at-risk individuals predict conversion to overt MS.[25] Adding more relevance to the need to consider spinal cord involvement in MS is the observation that such involvement may progress independently from the brain.[14] Given the time burden on the patient and health-care costs associated with spinal cord imaging, it is important to assess its utility in the evaluation of NEDA.

Previously, a 7-year longitudinal study evaluating NEDA in a real-world cohort using clinically obtained low-resolution 1.5T MRIs showed that 7% to 11% of patients with MS who developed MRI-defined disease activity in each of the years had disease activity on the spinal cord only.[6] Therefore, the goal of this study was to evaluate the diagnostic yield of combined brain and spinal cord 3T MRI in the evaluation of NEDA over a 1-year period.

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Methods

Patients

We prospectively studied 61 consecutive patients with MS from the Partners Multiple Sclerosis Center at Brigham and Women's Hospital (Boston, MA) who underwent MRI at baseline and 1 year later. Patient demographic and clinical data are summarized in Table 1. All the patients meet the International Panel criteria for either MS or a clinically isolated demyelinating syndrome.[26] Progression of Expanded Disability Status Scale (EDSS) score[27] was defined as an increase of 1.0 point or more at 6-month follow-up, which was required to be sustained at a clinic visit 6 months later (with the exception that if the EDSS score was 0 at baseline, a 1.5-point increase was required). At each clinic visit, patients had an evaluation of EDSS scores and anteceding relapses. During the observation period, 56 patients (91.8%) were already receiving DMT (monotherapy with intramuscular interferon beta [IFNβ]-1a [n = 20], subcutaneous IFNβ-1a [n = 11], IFNβ-1b [n = 1], glatiramer acetate [n = 20], natalizumab [n = 2], or mycophenolate mofetil [n = 1] or dual therapy with IFNβ-1a and mycophenolate mofetil [n = 1]). Of the 56 patients receiving DMT, 48 (85.7%) were receiving treatment for a mean ± SD of 4.8 ± 4.4 years (range, 0.1–14.1 years) at study entry. The other eight patients were newly started on DMT at the time of baseline MRI. There were three patients who had imaging at follow-up but were lost to clinical follow-up. All the patients signed an informed consent form; this study was approved by the Brigham and Women's Hospital research ethics committee.

***Table 1.* Demographic, clinical, and MRI data for the 61 study participants at baseline and 1-year follow-up**

Characteristic	Value
Age, mean ± SD (range), y	44.1 ± 8.6 (24–58)
Female sex, No. (%)	50 (82.0)
Clinical phenotype, No. (%)	
Clinically isolated demyelinating syndrome	3 (4.9)
Relapsing-remitting	56 (91.8)
Secondary progressive	2 (3.3)
Disease duration, mean ± SD (range), y[a]	10.5 ± 9.1 (0–35)
Timed 25-Foot Walk test at baseline, mean ± SD (range), s[b]	4.9 ± 1.1 (3.0–8.7)
EDSS score at baseline, mean ± SD (range)[b]	1.5 ± 1.6 (0–6)
Patients with spinal cord MRI lesions present at baseline, No. (%)	34 (55.7)
Clinical change at follow-up, No. (%)[b]	
Relapse on-study	11 (19.0)
EDSS score worsening at follow-up	7 (12.1)
No clinical activity on-study	41 (70.7)
NEDA on-study	28 (48.3)
MRI findings at follow-up, No. (%)	
NEDA by brain MRI	39 (63.9)
Activity by brain MRI	22 (36.1)
NEDA by spinal cord MRI	55 (90.2)
Activity by spinal cord MRI	6 (9.8)
NEDA by brain and spinal cord MRI	38 (62.3)
NEDA by brain MRI + activity by spinal cord MRI	1 (1.6)
Activity by brain MRI + NEDA by spinal cord MRI	17 (27.9)
Activity by brain and spinal cord MRI	5 (8.2)
Activity by brain or spinal cord MRI	23 (37.7)

Abbreviations: EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity by clinical or MRI change.
[a]Time from first symptoms.
[b]Three patients did not have clinical follow-up.

MRI Acquisition

All the patients underwent brain and spinal cord MRI at baseline and follow-up using a 3T scanner (GE Signa; GE Healthcare, Milwaukee, WI). Follow-up MRIs were obtained a mean ± SD of 12.4 ± 1.3 months (range, 9.7–15.2 months) after baseline. Brain and cervical images were obtained at both time points. Fifty patients also underwent thoracic spine imaging at both time points. The following imaging parameters were relevant to the present study: axial T2-weighted fluid-attenuated inversion recovery images of the brain (repetition time [TR] = 9000 milliseconds, echo time [TE] = 151 milliseconds, inversion time = 2250 milliseconds, pixel size = 0.976 × 0.976 × 2 mm; no interslice gaps), axial T2-weighted fast spin echo (FSE) images of the spinal cord (TR = 6166.66 milliseconds, TE = 110.24 milliseconds, voxel size = 0.937 × 0.937 × 3 mm; no interslice gaps), and sagittal T2-weighted FSE images of the spinal cord (TR = 3000 milliseconds, TE = 145.66 milliseconds, voxel size = 0.859 × 0.859 × 3 mm; no interslice gaps). Sample images are shown in Figure 1. Due to scan time limitations and the fact that these were research-related scans, intravenous gadolinium was not administered.

MRI Analysis

An experienced observer (ST) analyzed baseline and follow-up images concurrently using Jim software, version 7 (Xinapse Systems, West Bergholt, UK). Uncertain cases were reviewed by a senior observer (RB).

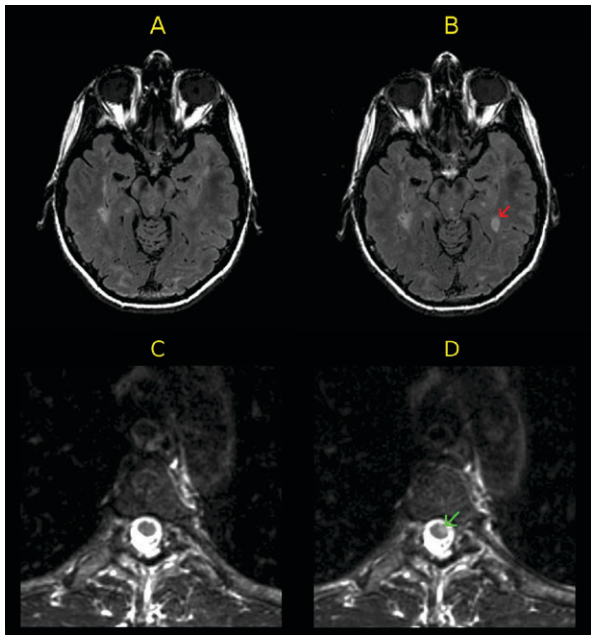

***Figure 1.* Examples of active magnetic resonance images (MRIs) at follow-up**

A and B, Baseline (A) and 1-year (B) axial fluid-attenuated inversion recovery (FLAIR) brain MRIs of a patient. The follow-up FLAIR MRI (B) shows a new T2 hyperintense brain lesion (red arrow) compared with baseline. C and D, Baseline (C) and 1-year (D) axial T2-weighted fast spin echo (FSE) thoracic spinal cord MRIs of another patient. The follow-up T2-weighted FSE MRI (D) shows a new T2 hyperintense lesion in the thoracic spinal cord (green arrow) compared with baseline.

Image window width and level were adjusted by the observer to ensure a consistent comparison between the two time points. The follow-up images were categorized qualitatively as active by the presence of either new or enlarging T2 hyperintense lesions. Thus, achieving NEDA by MRI was defined as no new or enlarging T2 hyperintense lesions. Examples of disease activity in the brain and spinal cord are shown in Figure 1.

Statistical Analysis

The proportions of patients who achieved NEDA in terms of lesion accumulation on brain MRI, lesion accumulation on spinal cord MRI, EDSS score progression, and relapse were estimated, and 95% confidence intervals (CIs) for each proportion were estimated using the exact binomial distribution. For the identification of disease activity using brain versus spinal cord lesions, the paired measurements were compared using the McNemar test. Furthermore, to estimate the additional diagnostic value of including spinal cord imaging, the proportion of patients who achieved NEDA in terms of lesion accumulation on brain MRI, EDSS score progression, or relapse but had disease activity on the spinal cord was calculated.

Results

Comparisons of patients achieving NEDA based on brain and spinal cord lesions are shown in Tables 1 and 2. Based on this sample of 61 patients, 63.9% (n = 39; 95% CI, 50.6%-75.8%) maintained NEDA in terms of brain MRI, whereas 90.2% (n = 55; 95% CI, 79.8%-96.3%) maintained NEDA based on spinal cord MRI. Thirty-eight patients achieved NEDA based on both brain and spinal cord MRI, and five patients had disease activity on both measures. Six patients had new spinal cord activity with new lesions at follow-up in the cervical only (n = 2), thoracic only (n = 3), or both (n = 1) regions of the spinal cord. The following spinal cord locations were involved with these new lesions: C2, C7, T6, T6-T7, T8-T9, and C4-C6, T4-T5, and T6 (Figure 1). Patients with disease activity in either the brain or spinal cord only were significantly more likely to have disease activity in the brain (P = .0001). In addition, only 1 of 39 patients who had NEDA based on brain MRI was identified as having disease activity based on the spinal cord (2.6%; 95% CI, 0.1%-13.5%), which can be considered the false-positive rate for NEDA based on the brain. However, this patient also had a clinical relapse that coincided with the new spinal cord activity. Thus, there was no case in which failure of NEDA was shown by spinal cord MRI alone. In total, there were seven patients with enlarging lesions, six of whom also had new lesions. At baseline, 34 patients (55.7%) had spinal cord lesions; 1 additional patient developed spinal cord involvement at follow-up.

Comparisons of patients achieving NEDA based on spinal cord lesions and relapses are shown in Table 3.

***Table 2.* Patients achieving NEDA at 1 year by brain and spinal cord MRI lesions**

	NEDA based on spinal cord lesions	Activity based on spinal cord lesions	Total
NEDA based on brain lesions	38	1	**39**
Activity based on brain lesions	17	5	**22**
Total	**55**	**6**	**61**

Abbreviations: MRI, magnetic resonance imaging; NEDA, no evidence of disease activity.
Note: Data are number of patients.

Comparisons of patients meeting the definition of NEDA based on spinal cord lesions and accumulation of physical disability (EDSS score) are shown in Table 4. Based on the 58 patients with clinical information, 81.0% (n = 47; 95% CI, 68.6%-90.1%) maintained NEDA in terms of relapses and 87.9% (n = 51; 95% CI, 76.7%-95.0%) maintained NEDA based on disability accumulation. In this slightly reduced sample, 91.4% of patients (n = 53; 95% CI, 81.0%-97.1%) maintained NEDA on spinal cord imaging. Forty-three patients maintained NEDA on both spinal cord imaging and relapses. Interestingly, 80% of the patients who had spinal cord activity at follow-up did not have an accompanying relapse. Four of 47 patients (8.5%; 95% CI, 2.4%-20.4%) who had NEDA based on relapses were identified as having disease activity on spinal cord MRI. When assessing patients who maintained NEDA on both spinal cord imaging and disability accumulation, 47 maintained NEDA on both measures, and only 1 patient had disease activity on both measures. Four of 51 patients (7.8%; 95% CI, 2.2%-18.9%) who achieved NEDA based on disability accumulation were identified as having disease activity in the spinal cord.

***Table 3.* Patients achieving NEDA at 1 year by spinal cord MRI lesions and relapses**

	NEDA based on spinal cord lesions	Activity based on spinal cord lesions	Total
NEDA based on relapses	43	4	**47**
Activity based on relapses	10	1	**11**
Total	**53**	**5**	**58**

Abbreviations: MRI, magnetic resonance imaging; NEDA, no evidence of disease activity.
Note: Data are number of patients.

***Table 4.* Patients achieving NEDA at 1 year by spinal cord lesions and disability accumulation**

	NEDA based on spinal cord lesions	Activity based on spinal cord lesions	Total
NEDA based on disability accumulation	47	4	**51**
Activity based on disability accumulation	6	1	**7**
Total	**53**	**5**	**58**

Abbreviation: NEDA, no evidence of disease activity.
Note: Data are number of patients.

Taken together, in decreasing order of sensitivity, the following rates of disease activity over 1 year were shown by the measures used in the present study: brain MRI activity (36.1%), clinical relapse (19.0%), worsening of EDSS score (12.1%), and spinal cord MRI activity (9.8%). More patients maintained NEDA in terms of clinical activity compared with brain and spinal cord imaging (70.7% vs. 62.3%). Overall, NEDA with the combination of clinical relapse, worsening of EDSS score, and brain MRI activity was maintained in 28 patients (48.3%) and remained the same with the addition of the spinal cord MRI findings.

Discussion

The spinal cord is a common site of pathology in MS, occurring early in the disease course[12,25] and playing a role in the development of disability[11,14-17,19,21-23,28]; such involvement includes overt multifocal inflammatory demyelinating lesions and the potential for tissue destruction (axonal loss/atrophy).[29] This study evaluated the role of brain and spinal cord 3T MRI in defining NEDA at 1 year. We showed that spinal cord MRI had a low diagnostic yield as an adjunct to brain MRI for defining NEDA. Only one patient had activity on spinal cord imaging while having NEDA on brain imaging. This patient also had an on-study relapse and would not have met NEDA regardless of the spinal cord MRI, further reducing the diagnostic yield of spinal cord imaging.

There are specific aspects of this patient population that may have reduced the yield of spinal cord imaging. Almost half of the patients were free of spinal cord lesions at baseline. This is a lower rate of spinal cord involvement than reported in other studies.[12,18] In addition, the present patients had a relatively long disease duration (on average, 10 years), whereas previous studies showing higher rates of spinal cord activity have reported patients with shorter disease duration.[12,18] In addition, most of the patients in this study had relapsing forms of MS. Studies have shown that these subtypes are less likely to have spinal cord involvement compared with patients with progressive forms of the disease.[30,31] Another important limitation of this study is the possibility that the results would have been different if a higher proportion of the study participants were taking the newer, higher-efficacy DMTs.[3,6] The absence of gadolinium administration is a limitation of this study in that the current definition of NEDA includes gado-

linium-enhancing lesions.[6] The sample size was small, which limited the statistical power of the study. This, combined with the other limitations, urges caution in the interpretation of the results and suggests that further studies with larger data sets are needed to confirm the findings.

Previous studies assessed NEDA in patients with MS using lower-field 1.5T MRI platforms.[2,3,6,32-37] Using brain and spinal cord 3T MRI in the present study, we found that nearly half of the patients maintained overall NEDA at 1 year, which was similar to other studies.[3,6,30,33,36] Approximately two-thirds of the patients in the present study had no MRI activity at 1 year; this was 50% to 60% in previous studies.[3,36,37] When considering only the clinical criteria for achieving NEDA, slightly more than two-thirds of the present patients met this definition; this was slightly higher (75% to 77%) in previous studies using newer, more potent DMTs than the present study.[3,36] Note that NEDA is still under investigation for its validity and is not yet considered a standard or primary outcome measure of disease status or therapeutic efficacy.

There are several potential strategies available to extend these findings regarding the utility of spinal cord MRI in defining NEDA. Patients with higher levels of disability, a higher proportion of spinal cord involvement, and a larger proportion with progressive forms of the disease than in the present study may show a greater role of spinal cord MRI. It would also be of interest to determine whether longer observation periods (ie, ≥2 years) would increase such a yield. This study evaluated the spinal cord with T2-weighted FSE, which is the clinical standard but may have a reduced sensitivity to lesions versus newer MRI sequences, such as short time inversion recovery and phase-sensitive inversion recovery.[38-43] Furthermore, the concept of NEDA is still evolving, with recent proposals to include brain volume loss and changes in neuropsychological test scores in the definition.[5,44] Thus, spinal cord atrophy may provide an additional tool to assess NEDA and complement lesion assessment, particularly given the proposed discordance between lesions and atrophy in a subset of patients with MS.[45] In addition, given that a recent study has shown a higher yield in the detection of spinal cord MS lesions at 7T versus 3T,[46] a high-resolution ultra-high-field approach may be more sensitive.

Considering that spinal cord imaging is a separate and distinct evaluation from a utilization standpoint, these findings suggest that this might not be necessary for routine monitoring. However, owing to the limitations of this study and general uncertainty about the role of NEDA, these results should not be directly used to change routine clinical practice. We would urge that further research is needed regarding the utility of spinal cord MRI in the routine monitoring of MS. □

PracticePoints

- We used 3T magnetic resonance imaging (MRI) to evaluate the role of the spinal cord as an adjunct to brain imaging in assessing disease activity in a real-world setting of patients with MS.
- Most patients had no activity on either brain (63.9%) or spinal cord (90.2%) MRI at 1 year.
- Of the 39 patients who had no activity on brain MRI, only 1 had spinal cord activity. This translates to a false-positive rate for no activity based on brain MRI of 2.6% (95% CI, 0.1%-13.5%).
- No evidence of disease activity was sustained in 48.3% of patients at 1 year and was the same with the addition of spinal cord MRI.

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