Should the symptomatic region be included in dissemination in space in MRI criteria for MS?

Wallace J. Brownlee,
FRACP
Josephine K. Swanton,
PhD
Katherine A. Miszkil,
FRCR
David H. Miller,
FMedSci
Olga Ciccarelli, FRCP

Correspondence to
Dr. Brownlee:
w.brownlee@ucl.ac.uk

ABSTRACT

Objectives: To investigate whether inclusion of lesions in the symptomatic region influences the performance of dissemination in space (DIS) criteria for a diagnosis of clinically definite multiple sclerosis (CDMS) in patients with a clinically isolated syndrome (CIS).

Methods: We studied 30 patients with CIS with brainstem/cerebellar and spinal cord syndromes who had MRI scans at the time of CIS and were followed up for the development of CDMS. We retrospectively applied the McDonald 2010 DIS criteria (excluding all lesions in the symptomatic region) to baseline MRI scans and 2 modified DIS criteria: (1) the inclusion of asymptomatic lesions in the symptomatic region in DIS, and (2) the inclusion of any lesion in the symptomatic region in DIS. The performance of the McDonald 2010 DIS criteria and the 2 modified criteria for the development of CDMS was compared.

Results: The sensitivity, specificity, and accuracy of the DIS criteria was, respectively, 73%, 73%, and 73% for the McDonald 2010 criteria, 80%, 73%, and 77% when asymptomatic lesions in the symptomatic region were included, and 87%, 73%, and 80% when any lesion in the symptomatic region was included in DIS.

Conclusions: Including lesions in the symptomatic region in DIS increases the sensitivity of MRI criteria for diagnosing multiple sclerosis without compromising specificity. These findings may help inform future revisions of the diagnostic criteria for multiple sclerosis.

Classification of evidence: This study provides Class II evidence that for patients with CIS, including lesions in the symptomatic region as part of the criteria for DIS does not significantly increase the accuracy for predicting the development of CDMS. The study lacks the precision to detect an important change in accuracy. *Neurology*® 2016;87:680-683

GLOSSARY

CDMS = clinically definite multiple sclerosis; **CIS** = clinically isolated syndrome; **DIS** = dissemination in space; **DIT** = dissemination in time; **MS** = multiple sclerosis.

A diagnosis of multiple sclerosis (MS) requires the demonstration of dissemination in space (DIS) and time (DIT). In people with a clinically isolated syndrome (CIS), the McDonald criteria^{1,2} allow the use of MRI to provide evidence of DIS and DIT rather than waiting for a second clinical attack.³ In patients with CIS, the McDonald criteria have an excellent sensitivity and specificity for the development of clinically definite MS (CDMS)⁴ and facilitate an earlier diagnosis of MS.⁵

In the 2010 revisions to the McDonald criteria, there was a major change in the requirements for DIS.⁶ The presence of one or more T2 hyperintense lesions in 2 of 4 anatomical regions typically affected in demyelination (periventricular, juxtacortical, infratentorial, spinal cord) provides MRI evidence for DIS.¹ When the patient's symptoms are referable to the brainstem/cerebellum or spinal cord, then lesions in the symptomatic region are excluded.^{1,6} However, the criteria are ambiguous as to whether all lesions in the symptomatic region should be excluded or only the symptomatic lesion.⁷

Editorial, page 652

From the Queen Square Multiple Sclerosis Centre (W.J.B., J.K.S., D.H.M., O.C.), Department of Neuroinflammation, UCL Institute of Neurology, London; Lysholm Department of Neuroradiology (K.A.M.), National Hospital for Neurology and Neurosurgery, London; and NIHR University College London Hospitals Biomedical Research Centre (D.H.M., O.C.), London, UK.

Go to *Neurology* for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The exclusion of lesions in the symptomatic region is not based on strong evidence, but rather a desire to maximize the specificity of MRI criteria by requiring lesions in 2 sites outside the symptomatic region to establish DIS. However, in previous diagnostic criteria for MS, whether clinical criteria³ or incorporating MRI,² symptomatic lesions have always contributed to DIS. The exclusion of lesions in the symptomatic region may reduce the sensitivity of the McDonald 2010 criteria in patients with brainstem/cerebellar and spinal cord syndromes,^{8,9} leading to delays in the diagnosis and management of MS. We wanted to investigate whether inclusion of lesions in the symptomatic region influences the sensitivity and specificity of DIS criteria for a diagnosis CDMS.

METHODS **Standard protocol approvals, registrations, and patient consents.** All patients provided written informed consent and the study was approved by the institutional ethics committee.

Patients. Thirty patients with CIS with brainstem/cerebellar and spinal cord syndromes were included. The patients were part of a larger prospective CIS cohort study described in detail previously.^{5,6} Briefly, patients aged between 16 and 50 years with typical CIS syndromes and no history of previous neurologic symptoms were eligible. T2-weighted and postcontrast T1-weighted scans of the brain and spinal cord were done at baseline (within 3 months of CIS) and brain imaging was repeated after 3 months. All scans were reviewed by a single neuroradiologist, blinded to the patient's clinical status. Lesion number, location, and gadolinium enhancement were noted. Patients were seen again at scheduled follow-up over the first 5 to 8 years after CIS. CDMS was diagnosed using the Poser criteria (i.e., a second clinical attack with evidence of 2 separate lesions).³

DIS criteria. We retrospectively applied 3 DIS criteria to the baseline MRI scans:

1. The McDonald 2010 DIS criteria¹
2. Modified criteria 1: The McDonald 2010 DIS criteria modified to include asymptomatic lesions in the symptomatic

region; for example, a well-defined cerebellar hemisphere lesion in a patient presenting with bilateral internuclear ophthalmoplegia, indicating a symptomatic lesion in the medial longitudinal fasciculus.

3. Modified criteria 2: The McDonald 2010 DIS criteria modified to include any lesion in the symptomatic region in DIS; for example, any spinal cord lesion in a patient presenting with a spinal cord syndrome.

We defined DIT using the 2010 McDonald criteria¹ (i.e., the presence of asymptomatic gadolinium-enhancing and nonenhancing lesions on a single scan or a new T2 lesion on the follow-up MRI) using the baseline and 3-month follow-up scans.

Statistical analysis. We calculated the sensitivity, specificity, and accuracy of the 3 DIS criteria (alone and in combination with DIT criteria) for the development of CDMS and 95% confidence intervals.⁶ We also calculated the times to diagnosis of MS based on clinical evidence alone (CDMS) or using the different MRI criteria (each requiring both DIS and DIT). The times to diagnosis of MS were not normally distributed and comparison was made using the 1-sample Wilcoxon signed rank test. All statistical analyses were done using SPSS version 21 (IBM Corp., Armonk, NY).

RESULTS The baseline demographic characteristics were typical of patients with a CIS (table 1). Over a mean follow-up period of 7.3 years, 15 (50%) developed CDMS. None of the patients received disease-modifying treatment before developing CDMS.

Twenty-three patients (77%) had one or more T2 hyperintense lesions in the symptomatic region. Twenty-two patients (73%) had an identifiable symptomatic lesion based on the neurologic examination findings, the presence of gadolinium enhancement, or both. Eleven patients (37%) had at least one asymptomatic lesion. The figure shows a Kaplan-Meier survival curve with the time to diagnosis of CDMS based on the number of lesions in the symptomatic region.

All of the DIS criteria, alone or in combination with DIT criteria, had good sensitivity and specificity for the development of CDMS (table 2). The 2 modified criteria were more sensitive and more accurate than the McDonald 2010 DIS criteria, and all 3 DIS criteria had the same specificity. The inclusion of any lesion in the symptomatic region had the highest overall sensitivity and accuracy for the development of CDMS.

The mean time to MS diagnosis for various diagnostic criteria (requiring both DIS and DIT) was as follows:

1. CDMS: 24.9 months
2. McDonald 2010 criteria: 8.9 months
3. DIS modified to include only asymptomatic lesions: 6.7 months
4. DIS modified to include any lesion: 4.8 months

Although using the modified DIS allowed a shorter time to diagnosis of MS compared with the time to CDMS ($p < 0.001$), the time to diagnosis was not significantly different when compared with the McDonald 2010 criteria.

Table 1 Baseline patient characteristics

	Brainstem/cerebellar syndrome (n = 20)	Spinal cord syndrome (n = 10)	All patients (n = 30)
Age, y, mean (SD)	30.6 (8.3)	32.6 (9.9)	31.25 (8.8)
Female, n (%)	14 (70)	4 (40)	18 (60)
No. of lesions in the symptomatic site			
Normal MRI	5	2	7
1 lesion	9	3	12
2 or more lesions	6	5	11
Baseline EDSS score, median	2.25	2	2

Abbreviation: EDSS = Expanded Disability Status Scale.

Figure Time to diagnosis of multiple sclerosis

Kaplan-Meier survival curve showing time to diagnosis of clinically definite multiple sclerosis based on the number of T2 hyperintense lesions in the symptomatic region. CDMS = clinically definite multiple sclerosis; CIS = clinically isolated syndrome.

DISCUSSION We found that the inclusion of lesions in the symptomatic region in patients with clinically isolated brainstem/cerebellar and spinal cord syndromes increased the sensitivity and accuracy of DIS criteria for a diagnosis of CDMS without compromising specificity.

The Magnetic Resonance Imaging in Multiple Sclerosis Group has recently recommended revisions to the MRI criteria for DIS to include lesions in the symptomatic region.¹⁰ This study provides evidence to support that recommendation. We found that inclusion of both asymptomatic and symptomatic lesions in the symptomatic region increased the sensitivity of DIS criteria for the development of CDMS. However, we would favor modified DIS criteria that include any lesion in the symptomatic region, first

because the sensitivity was higher and second because the criteria would be easier to apply in a clinical setting. Determining whether a lesion is symptomatic or asymptomatic is sometimes difficult and not always possible.

Some limitations need to be noted. First, patients included in this study had syndromes that were typical of a first demyelinating event, such as bilateral internuclear ophthalmoplegia and partial myelitis.¹¹ The McDonald MRI criteria should only be applied to patients with typical CIS syndromes and care should be taken to exclude conditions that might mimic MS. Second, over a follow-up period of 7 years, half of the cohort developed CDMS. With longer follow-up, this number may increase, potentially influencing the performance of the MRI criteria, although more than half of patients with CIS who develop MS have a second clinical attack in the first 5 years of follow-up.¹⁰ Finally, we tested the 2 modified DIS criteria in a relatively small cohort of patients. Although we found an increase in sensitivity and accuracy using the modified DIS criteria, the confidence intervals are wide, reflecting the small size of the cohort. However, the results are encouraging and the criteria should be tested in a larger multicenter CIS cohort to inform future changes to the diagnostic criteria for MS.

AUTHOR CONTRIBUTIONS

Dr. Brownlee contributed to study concept/design, analysis and interpretation of data, statistical analysis, and drafting the manuscript. Dr. Swanton contributed to acquisition of data and revision of the manuscript. Dr. Miskiel contributed to acquisition of data and revision of the manuscript. Dr. Miller obtained funding and contributed to study concept/design and revision of the manuscript. Dr. Ciccarelli contributed to study concept/design, revision of the manuscript, and provided study supervision.

STUDY FUNDING

The study was supported by the United Kingdom MS Society (grant 995) and the Neurologic Foundation of New Zealand (grant 1207-CF). The Queen Square MS Centre is supported by the United Kingdom MS Society and the NIHR University College London Hospitals Biomedical Research Centre.

DISCLOSURE

W. Brownlee, J. Swanton, and K. Miskiel report no disclosures relevant to the manuscript. D. Miller has received honoraria through payments to UCL Institute of Neurology from Biogen Idec, Novartis, Bayer Schering, and Mitsubishi Pharma Europe. Dr. Miller receives royalties from the publication of *McAlpine's Multiple Sclerosis*, 4th edition. O. Ciccarelli is a consultant for Novartis, Biogen Idec, Genzyme, and General Electric, and all the payments are made to the UCL Institute of Neurology. She is an associate editor of *Neurology*. Go to Neurology.org for full disclosures.

Received November 6, 2015. Accepted in final form April 22, 2016.

REFERENCES

- Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.

Table 2 Performance of the McDonald 2010 DIS criteria and the modified DIS criteria for the development of clinically definite multiple sclerosis

	Sensitivity (95% CI), %	Specificity (95% CI), %	Accuracy (95% CI), %
DIS criteria only			
McDonald 2010 DIS criteria	73 (45–92)	73 (45–92)	73 (54–87)
Modified criteria 1	80 (51–96)	73 (45–92)	77 (57–90)
Modified criteria 2	87 (60–98)	73 (45–92)	80 (61–92)
DIS + DIT criteria combined			
McDonald 2010 criteria	67 (39–88)	73 (45–92)	70 (50–84)
Modified criteria 1	73 (45–92)	73 (45–92)	73 (54–87)
Modified criteria 2	80 (51–96)	73 (45–92)	77 (57–90)

Abbreviations: CI = confidence interval; DIS = dissemination in space; DIT = dissemination in time.

2. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." *Ann Neurol* 2005;58:840–846.
3. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;13:227–231.
4. Gomez-Moreno M, Diaz-Sanchez M, Ramos-Gonzalez A. Application of the 2010 McDonald criteria for the diagnosis of multiple sclerosis in a Spanish cohort of patients with clinically isolated syndromes. *Mult Scler* 2012;18:39–44.
5. Brownlee WJ, Swanton JK, Altmann DR, Ciccarelli O, Miller DH. Earlier and more frequent diagnosis of multiple sclerosis using the McDonald criteria. *J Neurol Neurosurg Psychiatry* 2015;86:584–585.
6. Swanton JK, Fernando K, Dalton CM, et al. Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. *J Neurol Neurosurg Psychiatry* 2006;77:830–833.
7. Rovira A, Wattjes MP, Tintore M, et al. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—clinical implementation in the diagnostic process. *Nat Rev Neurol* 2015;11:471–482.
8. Kang H, Metz LM, Traboulsee AL, et al. Application and a proposed modification of the 2010 McDonald criteria for the diagnosis of multiple sclerosis in a Canadian cohort of patients with clinically isolated syndromes. *Mult Scler* 2014;20:458–463.
9. Ruet A, Deloire MS, Ouallat JC, Molinier S, Brochet B. Predictive factors for multiple sclerosis in patients with clinically isolated spinal cord syndrome. *Mult Scler* 2011;17:312–318.
10. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain* 2008;131:808–817.
11. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol* 2016;15:292–303.

Share Your Artistic Expressions in *Neurology* 'Visions'

AAN members are urged to submit medically or scientifically related artistic images, such as photographs, photomicrographs, and paintings, to the "Visions" section of *Neurology*[®]. These images are creative in nature, rather than the medically instructive images published in the *NeuroImages* section. The image or series of up to six images may be black and white or color and must fit into one published journal page. Accompanying description should be 100 words or less; the title should be a maximum of 96 characters including spaces and punctuation.

Learn more at www.aan.com/view/Visions, or upload a Visions submission at submit.neurology.org.

Neurology[®] Genetics Call For Papers

Neurology: Genetics is an open access, online only journal that provides neurologists with outstanding original contributions that elucidate the role of genetic and epigenetic variation in diseases and biological traits of the central and peripheral nervous system. We welcome all submissions. For more information on how to submit, visit <http://www.neurology.org/site/gen/gen2.xhtml>.