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Application of the 2010 revised criteria for the diagnosis of multiple sclerosis to patients with clinically isolated syndromes

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Background and purpose: Recently, the McDonald criteria for the diagnosis of multiple sclerosis (MS) have been revised, with the aims to diagnose earlier and to simplify the use of brain MRI. To validate the 2010 revised criteria they were applied to a cohort of patients with clinically isolated syndromes (CIS).

Methods: In all, 178 CIS patients were followed from onset. Test characteristics were calculated after 1, 3 and 5 years and compared between the 2005 and 2010 revised criteria. The time to diagnosis of the 2005 and 2010 criteria was compared using survival analysis and the log-rank test. Clinical evidence for dissemination in space and time was the gold standard for clinically definite MS (CDMS).

Results: During follow-up, 76 patients converted to CDMS (mean time to conversion 23.9 months). At 1 year, the specificity and accuracy of the 2005 criteria were a little higher than those of the 2010 criteria (98.0% and 98.4% vs. 86.3% and 88.5%). However, at 5 years, differences completely disappeared (specificity 85.7% and accuracy 93.3% for both criteria). MS diagnosis could be made significantly faster with the 2010 criteria ($P = 0.007$). Using the 2010 criteria, in 19% of patients the diagnosis could already be made at baseline.

Conclusions: By applying the 2010 revised criteria a diagnosis of MS can be made earlier, whilst prediction of disease progression is maintained. This validation brings along great advantages, for treatment possibilities as well as patient counselling.

Introduction

Since the publication of the Poser criteria in 1983 [1], the diagnosis of multiple sclerosis (MS) has been based on the demonstration of dissemination in space (DIS) and time (DIT): evidence that the disease has affected more than one part of the central nervous system on more than one occasion.

Patients with MS often present with a first episode of symptoms suggestive for demyelination, such as optic neuritis or transverse myelitis. This first episode is called clinically isolated syndrome (CIS). MS is a disabling disease that affects especially young people in the prime of their lives. Patients with CIS face a very insecure future, not knowing whether or not they will go on to develop MS and, if they do, how the disease course will be [2]. To be able to advise CIS patients as well as possible, it is very important that a diagnosis of MS can be made quickly and accurately. Also, the possibility of starting appropriate treatment early may be beneficial for disease outcome in MS [3].

For these reasons, several attempts have been made over the years to adjust the criteria in such a way that the diagnosis of MS can be made earlier and more easily. Several revisions to the diagnostic criteria have been published by the International Panel on the Diagnosis of MS. In 2001, the MRI scan was added as an important diagnostic tool that could be used for the criterion of DIS [4]. In 2005 [5] and 2010 [6], the criteria were revised again. The revised diagnostic criteria of 2005 and 2010 for relapsing–remitting MS are shown in Table 1.

In the latest revisions of 2010, aims were to simplify the use of brain MRI for the diagnosis of MS and to allow for earlier diagnosis in different populations. As can be seen from the table, with these criteria the diagnosis of MS can sometimes already be made in patients with only a single attack (CIS), after a single baseline brain MRI scan. If these criteria prove to work well, this would be a huge progress in the diagnostics of MS. However, the risk of false positive diagnoses is not imaginary. For example, in a study by Chard *et al.* [7] it has been shown that 10%–15%

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Table 1 Overview of revisions of the diagnostic criteria for MS

	McDonald 2005	McDonald 2010
DIS	Objective clinical evidence of ≥2 lesions, or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack involving a different CNS site ≥3 of the 4 Barkhof–Tintoré criteria fulfilled: ≥9 T2 hyperintense lesions or 1 gadolinium-enhancing lesion ≥3 periventricular lesions ≥1 juxtacortical lesion ≥1 infratentorial lesion (1 spinal cord lesion can substitute for 1 brain lesion and spinal cord lesions can be included in the total T2 lesion count) ≥2 T2 lesions plus positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)	Objective clinical evidence of ≥2 lesions, or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack involving a different CNS site ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (Swanton criteria): Periventricular Juxtacortical Infratentorial Spinal cord (symptomatic lesions in patients with brainstem or spinal cord syndrome are excluded)
DIT	≥2 attacks separated by a period of at least 1 month 1 gadolinium-enhancing lesion ≥3 months after CIS if not at the site corresponding to CIS A new T2 lesion compared with a previous scan obtained ≥30 days after CIS	≥2 attacks separated by a period of at least 1 month Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time A new T2 and/or gadolinium-enhancing lesion on follow-up MRI, irrespective of its timing with reference to a baseline scan

DIS, dissemination in space; DIT, dissemination in time; CNS, central nervous system; CSF, cerebrospinal fluid; CIS, clinically isolated syndrome; MRI, magnetic resonance imaging. Based on 2005 revisions to the McDonald criteria [5] and 2010 revisions to the McDonald criteria [6].

of patients that were diagnosed with MS based on the 2005 MRI criteria never had a clinical second attack in up to two decades.

To investigate what the 2010 criteria really add to the existing diagnostics in MS, their accuracy was investigated and compared with the 2005 criteria by applying them to our cohort of CIS patients.

Patients and methods

Patients

Patients were included in the neurology outpatient clinic of the Erasmus MC University Hospital, a tertiary referral centre for MS patients. In our centre, all patients aged 18–50 years with a first episode suggestive for demyelination are followed prospectively if they give informed consent (approved by the Erasmus MC ethics committee). For the present study, all patients were included who had experienced a first episode suggestive of demyelination, had a baseline MRI scan performed within 3 months of symptom onset and had at least 1 year of follow-up. All patients were clinically assessed at baseline and thereafter seen regularly for reassessment. Exacerbation was defined as a worsening of existing symptoms or the appearance of new symptoms lasting for more than 24 h, after a period of more than 30 days of improvement or stability, confirmed by neurological examination [8]. A temporary neurological deterioration associated with fever was not considered as an exacerbation. Clinically definite MS (CDMS) was diagnosed when there was clinical evidence for DIS and DIT as described by Poser and colleagues [1]. This was used as the gold standard for the diagnosis of multiple sclerosis. At baseline, MRI and laboratory tests were performed to rule out alternative diagnoses. This was repeated during follow-up if necessary. Patients with alternative diagnoses were not included in the analyses.

Procedures

All brain MRI scans were performed on 1.5 T scanners with a standard head coil (Philips, Best, The Netherlands, or General Electric, Milwaukee, WI, USA). Scans typically consisted of an axial T1-weighted sequence, an axial spin echo proton-density-weighted (PDW) and a T2-weighted sequence, and an axial fluid-attenuated inversion recovery (FLAIR) sequence, with 2–5 mm images. Post-gadolinium T1-weighted sequences were added by the radiologist on indication in patients with T2 lesions suggestive of demyelination. Since spinal cord scans were not systematically performed, these were not included in the analysis.

Baseline scans were scored for Barkhof–Tintoré criteria and Swanton criteria for DIS, and for criteria for DIT according to the 2010 revisions to the McDonald criteria. These criteria are described in Table 1.

Statistical methods

The following test characteristics were calculated.

Sensitivity: the proportion of patients with the disease who have a positive test result. This was calculated as true positives/(true positives + false negatives).

Specificity: the proportion of patients without the disease who have a negative test result. This was calculated as true negatives/(true negatives + false positives).

Positive predictive value (PPV): the proportion of patients who have the disease amongst the patients with positive test results. This was calculated as true positives/(true positives + false positives).

Accuracy: the proportion of true results of a test. This was calculated as (true positives + true negatives)/(true positives + false positives + true negatives + false negatives).

Test characteristics for the criteria for DIS of the 2005 and 2010 criteria and for DIT of the 2010 criteria based on the baseline scan were calculated after 1, 3 and 5 years of follow-up. For the calculations regarding MRI criteria for DIT at baseline according to the 2010 criteria, only patients for whom post-gadolinium images were available or scans that showed no abnormalities were taken into account (n = 114).

Test characteristics of the 2010 diagnostic criteria (DIS + DIT) were calculated after 1, 3 and 5 years of follow-up and compared with the 2005 criteria. For these calculations, only patients who had at least one follow-up scan were included in the analyses (n = 61).

Time to diagnosis with the 2005 and 2010 criteria was analysed using Kaplan–Meier survival analyses and compared with a log-rank test. Survival analysis included all patients with a follow-up scan and/or a diagnosis of MS according to 2010 criteria.

Statistical analyses were performed using SPSS version 17.0 for Windows.

Results

Patients

In all, 187 patients from our CIS cohort met the inclusion criteria. Nine patients (4.8%) were diagnosed with diseases other than MS (four neuromyelitis optica, two Leber's hereditary optic neuropathy, one chronic relapsing inflammatory optic neuropathy, one vascular, one psychogenic); these patients were not included in the analysis, which left 178 patients eligible for analysis (Fig. 1). Median follow-up time of the patients was 44.5 months (range 12–174). Baseline characteristics of the included patients are shown in Table 2. Seventy-six patients (42.7%) had at least one relapse during follow-up leading to the diagnosis of CDMS. Mean time to conversion was 23.9 months (median 16.5, range 1–86). Twenty-four patients (13.5%) received immune-modulating therapy before they had a second clinical attack. Sixty-one patients (34.3%) had at least one follow-up MRI scan.

DIS and DIT criteria of baseline scans

When comparing the 2005 and 2010 criteria for DIS, the following could be seen in our cohort (see also Fig. 1 and Table 3A).

Seventy-two of 178 patients (40.4%) fulfilled the Barkhof–Tintoré criteria; 125 patients (70.2%) fulfilled DIS 2005 criteria including cerebrospinal fluid (CSF). Sixty-seven (53.6%) of the DIS 2005 positive patients converted to CDMS during follow-up. Nine (17.0%) of 53 patients who did not fulfil DIS 2005 criteria converted to CDMS during follow-up. The

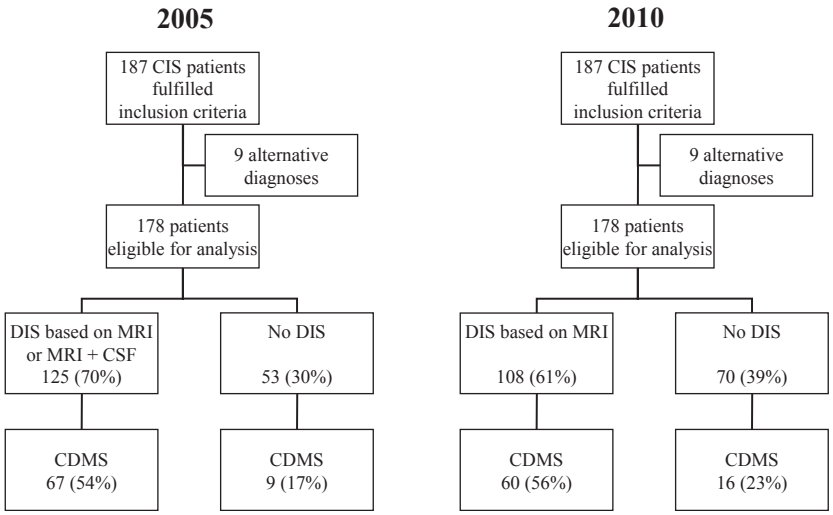

Figure 1 Flowcharts of patients in analysis and percentages of patients in the different groups with CDMS during follow-up; left, 2005 revised criteria; right, 2010 revised criteria. DIS, dissemination in space; DIT, dissemination in time; CDMS, clinically definite multiple sclerosis.

Table 2 Characteristics of patients (n = 178)

Characteristic	N (%)
Gender	
Male	52 (29.2)
Female	126 (70.8)
Ethnicity	
Caucasian	168 (94.4)
Asian	1 (0.6)
Black	3 (1.7)
Mediterranean	6 (3.4)
Clinical syndrome	
Optic neuritis	74 (41.6)
Brainstem	27 (15.2)
Spinal cord	39 (21.9)
Cerebellum	9 (5.1)
Cerebral hemispheres	20 (11.2)
Other	9 (5.1)
CDMS	76 (42.7)
Age at onset (years)	Mean 32.7, median 33.0 (range 16–54)
Time to baseline MRI (weeks)	Mean 4.8, median 4.0 (range 0–13)
Follow-up time (months)	Mean 51.7, median 44.5 (range 12–174)
Time to CDMS (months)	Mean 23.9, median 16.5 (range 1–86)

CDMS, clinically definite multiple sclerosis.

sensitivity of the DIS 2005 criteria was 88.2% (95% CI 80.9–95.4) and the specificity was 43.1% (95% CI 33.5–52.8). The PPV for DIS 2005 was 53.6% (95% CI 44.9–62.3) and the accuracy 62.4% (95% CI 55.2–69.5).

The Swanton criteria for DIS as used in the 2010 revisions to the McDonald criteria were fulfilled in 108 (60.7%) of our patients. Sixty (55.6%) of them developed CDMS during follow-up. Sixteen (22.9%) of 70 patients who did not fulfil the Swanton DIS 2010 criteria converted to CDMS. The sensitivity of the Swanton criteria was 79.0% (95% CI 69.8–88.1) and the specificity was 52.9% (95% CI 43.3–62.6). The PPV and accuracy were 55.6% (95% CI 46.2–64.9) and 64.0% (95% CI 57.0–71.1), respectively.

When examining the 2010 criteria for DIT, it was found that 36 (31.6%) of 114 patients fulfilled the criteria at baseline. Sixteen (44.4%) of them converted to CDMS during follow-up. Twenty-seven (34.6%) of 78 patients who did not fulfil the new DIT criteria converted to CDMS. The sensitivity of the DIT criteria was 37.2% (95% CI 22.8–51.7) and the specificity was 71.8% (95% CI 61.4–82.3). Thirty-three (18.5%) patients fulfilled criteria for both DIS and DIT 2010 at baseline.

2010 vs. 2005 revised criteria

Of the 61 patients for whom a follow-up scan was available, 43 (70.5%) had the diagnosis MS according

Table 3 Test characteristics of criteria for DIS and DIT of baseline scans (A) and for 2005 and 2010 criteria as a whole (B)

	A			B	
	DIS 2005 (Barkhof–Tintoré + CSF)	DIS 2010 (Swanton)	DIT 2010 Baseline MRI	2005 DIS + DIT (n = 61)	2010 DIS + DIT (n = 61)
Sensitivity					
1 year (n = 178)	92.3% (82.1–100)	80.8% (65.6–95.9)	62.5% (38.8–86.2)		
3 years (n = 110)	92.3% (83.9–100)	84.6% (73.3–95.9)	52.4% (31.0–73.7)		
5 years (n = 54)	84.4% (71.8–97.0)	84.4% (71.8–97.0)	61.5% (35.1–88.0)		
Total follow-up (n = 178)	88.2% (80.9–95.4)	79.0% (69.8–88.1)	37.2% (22.8–51.7)		
Specificity					
1 year (n = 178)	33.6% (26.1–41.1)	42.8% (34.9–50.6)	73.5% (64.7–82.2)	98.0% (94.2–100)	86.3% (76.8–95.7)
3 years (n = 110)	31.0% (20.2–41.7)	47.9% (36.3–59.5)	76.7% (64.1–89.4)	91.7% (80.6–100)	87.5% (74.3–100)
5 years (n = 54)	31.8% (12.4–51.3)	54.6% (33.7–75.4)	90.9% (73.9–100)	85.7% (67.4–100)	85.7% (67.4–100)
Total follow-up (n = 178)	43.1% (33.5–52.8)	52.9% (43.3–62.6)	71.8% (61.4–82.3)	78.3% (61.4–95.1)	73.9% (56.0–91.9)
PPV					
1 year (n = 178)	19.2% (12.3–26.1)	19.4% (12.0–26.9)	27.8% (13.2–42.4)	90.9% (73.9–100)	58.8% (35.4–82.2)
3 years (n = 110)	42.4% (31.9–52.9)	47.1% (35.5–58.8)	52.4% (31.0–73.7)	90.5% (77.9–100)	86.4% (72.0–100)
5 years (n = 54)	64.3% (49.8–78.8)	73.0% (58.7–87.3)	88.9% (68.4–100)	88.9% (74.4–100)	88.9% (74.4–100)
Total follow-up (n = 178)	53.6% (44.9–62.3)	55.6% (46.2–64.9)	50.0% (30.8–69.2)	88.4% (78.8–98.0)	86.4% (76.2–96.5)
Accuracy					
1 year (n = 178)	42.1% (34.9–49.4)	48.3% (41.0–55.7)	71.9% (63.7–80.2)	98.4% (95.2–100)	88.5% (80.5–96.5)
3 years (n = 110)	52.7% (43.4–62.1)	60.9% (51.8–70.0)	68.8% (57.4–80.1)	95.4% (89.1–100)	93.0% (85.4–100)
5 years (n = 54)	63.0% (50.1–75.8)	72.2% (60.3–84.2)	75.0% (57.7–92.3)	93.3% (84.4–100)	93.3% (84.4–100)
Total follow-up (n = 178)	62.4% (55.2–69.5)	64.0% (57.0–71.1)	58.8% (49.7–67.8)	91.8% (84.9–98.7)	90.2% (82.7–97.6)

PPV, positive predictive value; DIS, dissemination in space; DIT, dissemination in time; CSF, cerebrospinal fluid. For (B), only patients for whom a second scan was available were taken into account. Test characteristics are shown at 1, 3 and 5 years of follow-up and total follow-up.

to the 2005 criteria, with a mean time to diagnosis of 26.1 months (SD 22.4). Forty-four (72.1%) patients received the diagnosis MS according to the 2010 criteria, with a mean time to diagnosis of 23.6 months (SD 24.0). Thirty-eight of those patients had a second clinical attack during follow-up leading to CDMS. Mean time to CDMS was 27.9 months (SD 23.9).

At 1 year of follow-up, 58.8% of patients who were diagnosed with MS according to the 2010 criteria had had a second clinical attack leading to CDMS. At 3 years, this was 86.4%. At 5 years of follow-up, 18 of 30 patients (60.0%) were diagnosed with MS according to the 2010 criteria. At this time, 16 (53.3%) patients had CDMS; so at 5 years two patients (6.7%) who had the MS diagnosis based on 2010 criteria would still never have had a second clinical attack. However, one of these two patients had a second clinical attack at 5 years and 4 months after CIS. The PPV of the 2010 criteria increases from 58.8% at 1 year to 86.4% at 3 years and 88.9% at 5 years. The specificity at 1, 3 and 5 years is 86.3%, 87.5% and 85.7%, respectively. The specificity (and thus also the number of false positives) of the 2010 criteria at 5 years is the same as for the 2005 criteria.

The test characteristics are shown in Table 3B.

The survival curves of time to diagnosis with the 2005 and 2010 criteria are depicted in Fig. 2; the main difference is the much larger number of diagnoses made at baseline with the 2010 criteria, with a steep drop at this point. Time to diagnosis between the two methods differed significantly ($P = 0.007$).

Discussion

In this study the performance of the new diagnostic criteria for MS was investigated. The criteria for DIS and DIT used in the 2005 and 2010 criteria in our cohort of 178 CIS patients were also tested with an average follow-up time of over 4 years.

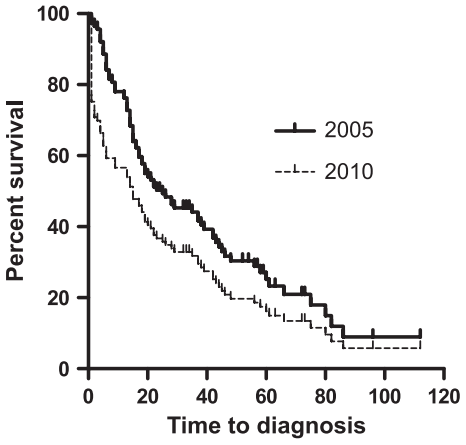

Figure 2 Survival curve of time to diagnosis with the two criteria: the 2010 criteria allow for earlier diagnosis.

Many studies have calculated test characteristics for the Barkhof–Tintoré criteria [9–18]. To be able to better compare DIS criteria in the 2005 and 2010 revisions to the diagnostic criteria for MS, the test characteristics for DIS 2005 were calculated including both Barkhof–Tintoré criteria and CSF analysis. In doing so, a relatively high sensitivity (88.2%) for DIS 2005 was found compared with other studies, but a lower specificity (43.1%) [9–18]. The DIS 2010/Swanton criteria showed a somewhat lower sensitivity (79.0%) and a higher specificity (52.9%) compared with DIS 2005. Overall, the DIS criteria of 2005 and 2010 performed similarly in the prediction of CDMS (accuracy 62.4% and 64.0%). The new criteria for DIT had a reasonable specificity (71.8%) but a low sensitivity (37.2%), in our study even somewhat lower than in the study by Gomez-Moreno *et al*. [18].

When comparing the 2005 and 2010 criteria taking both DIS and DIT into account, a somewhat lower specificity was found for the 2010 criteria (73.9%) compared with the 2005 criteria (78.3%), and a similar PPV (86.4% vs. 88.4%). However, it should be noted that the PPV for the 2010 criteria strongly increases with follow-up time, whereas it remains stable for the 2005 criteria (as shown in Table 3): at 1 year, specificity and PPV of the 2005 criteria were a little higher than those of the 2010 criteria, but at 5 years differences were completely gone. This reflects the fact that in many patients a diagnosis can be made much earlier with the 2010 criteria, whilst some of them will have their second clinical attack only many years later. So, the longer the follow-up time is, the better the test characteristics for the 2010 criteria get. In our cohort, after 5 years only two patients got a diagnosis of MS with the new criteria but did not experience a second clinical attack ('false positives'). One of them did have a second clinical attack but after 5 years and 4 months of follow-up, so the number of false positives would decrease even further with increasing follow-up time.

At 5 years of follow-up, the number of false positives for both diagnostic methods is the same, but diagnosis was made significantly faster with the 2010 criteria. For a serious disease with such a considerable impact on one's life as MS, it is of great importance to have as few false positives as possible. However, it is also very valuable to be able to give a patient some certainty early in a disease process that brings already many uncertainties with it. Also, an early diagnosis allows for earlier treatment, which may be beneficial for disease outcome [3], although it might be debat-

able if this is really an advantage for patients who turn out to have a mild disease course.

Since the introduction of the 2010 revisions, the CSF examination is no longer included in the diagnostic criteria for relapsing–remitting MS. However, as is acknowledged, CSF can still be important to evaluate alternative diagnoses [6,19]. This was not tested in this study because of the low number of patients with alternative diagnoses in our cohort. Those patients were excluded from the analyses.

There are some shortcomings to our study. Not all patients underwent spinal cord MRI and not all patients had a follow-up MRI scan performed. For this reason, test characteristics for the 2005 and 2010 criteria as a whole were calculated in the subgroup of patients for whom a second scan was available. A small number of patients (13.5%) received immunemodulating therapy before a second attack. These 'high risk' patients were not excluded from this study because they would probably have provided more bias if they were excluded than now being included.

In this cohort, the frequency of diagnoses other than MS was low (4.8%). In this situation, specificity (reflecting the proportion of patients without the disease that have a negative test result) functions to differentiate between monophasic and progressive disease, more than between MS and other diagnoses. To be noted, other studies testing diagnostic criteria for MS have also excluded alternative diagnoses [14,15,20]. It remains questionable whether the criteria that work well in such cohorts retain their specificity when applied to populations in general hospitals. At least for the Swanton criteria for DIS, this seems to be the case [21]. Still, it should be emphasized, especially for use in more general patient populations, that it is always necessary to rule out alternative diagnoses first.

In a cohort of 178 patients it was shown that the diagnosis of MS could be made easier and faster with the 2010 revised criteria compared with the 2005 criteria. One other study applied the 2010 criteria to a cohort of CIS patients [18] and, although in this study no follow-up scans were included, it also confirmed the value of the new criteria. As recent posters at the ECTRIMS congress showed (e.g. [22], ECTRIMS 2012), the new criteria are starting to be validated globally. In our cohort, in a substantial number of CIS patients (33; 18.5%) the diagnosis could already be made at baseline. Test characteristics of the 2010 and 2005 criteria are similar, but because test characteristics of 2010 criteria increase with follow-up time, those criteria might perform better when tested in a cohort with an even longer follow-up time. The fact that the diagnosis of MS can be made earlier with the 2010 criteria is a great advantage, giving CIS patients at least a glimpse of certainty after a life-changing event.

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Disclosures of conflict of interest

The authors declare no financial or other conflict of interest.

References

1. Poser CM, Paty DW, Scheinberg L, *et al.* New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; **13:** 227–231.
2. Degenhardt A, Ramagopalan SV, Scalfari A, Ebers GC. Clinical prognostic factors in multiple sclerosis: a natural history review. *Nat Rev Neurol* 2009; **5:** 672–682.
3. Freedman MS. Long-term follow-up of clinical trials of multiple sclerosis therapies. *Neurology* 2011; **76:** S26–S34.
4. 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. *Ann Neurol* 2001; **50:** 121–127.
5. 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.
6. 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.
7. Chard DT, Dalton CM, Swanton J, *et al.* MRI only conversion to multiple sclerosis following a clinically isolated syndrome. *J Neurol Neurosurg Psychiatry* 2011; **82:** 176–179.
8. Schumacher GA, Beebe G, Kibler RF, *et al.* Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann N Y Acad Sci* 1965; **122:** 552–568.
9. 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** (Pt 11) **:** 2059–2069.
10. Rovira A, Swanton J, Tintore M, *et al.* A single, early magnetic resonance imaging study in the diagnosis of multiple sclerosis. *Arch Neurol* 2009; **66:** 587–592.
11. Tintore M, Rovira A, Brieva L, *et al.* Isolated demyelinating syndromes: comparison of CSF oligoclonal bands and different MR imaging criteria to predict conversion to CDMS. *Mult Scler* 2001; **7:** 359–363.
12. Diaz-Sanchez M, Mayra G-MS, Asuncion M-OM, *et al.* Accuracy of MRI criteria for dissemination in space for the diagnosis of multiple sclerosis in patients with clinically isolated syndromes. *Mult Scler* 2010; **16:** 576–580.

13. Tintore M, Rovira A, Martinez MJ, *et al*. Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. *AJNR Am J Neuroradiol* 2000; **21:** 702–706.
14. Swanton JK, Rovira A, Tintore M, *et al*. MRI criteria for multiple sclerosis in patients presenting with clinically isolated syndromes: a multicentre retrospective study. *Lancet Neurol* 2007; **6:** 677–686.
15. Dalton CM, Brex PA, Miszkiel KA, *et al*. Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis. *Ann Neurol* 2002; **52:** 47–53.
16. Masjuan J, Alvarez-Cermeno JC, Garcia-Barragan N, *et al*. Clinically isolated syndromes: a new oligoclonal band test accurately predicts conversion to MS. *Neurology* 2006; **66:** 576–578.
17. Villar LM, Garcia-Barragan N, Sadaba MC, *et al*. Accuracy of CSF and MRI criteria for dissemination in space in the diagnosis of multiple sclerosis. *J Neurol Sci* 2008; **266:** 34–37.
18. 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.
19. Tumani H, Deisenhammer F, Giovannoni G, *et al*. Revised McDonald criteria: the persisting importance of cerebrospinal fluid analysis. *Ann Neurol*. 2011; **70:** 520; author reply 521.
20. Korteweg T, Tintore M, Uitdehaag B, *et al*. MRI criteria for dissemination in space in patients with clinically isolated syndromes: a multicentre follow-up study. *Lancet Neurol* 2006; **5:** 221–227.
21. Nielsen JM, Uitdehaag BM, Korteweg T, *et al*. Performance of the Swanton multiple sclerosis criteria for dissemination in space. *Mult Scler* 2010; **16:** 985–987.
22. Montalban X, Kappos L, Freedman MS, et al. Application of the revised version of the 2010 McDonald diagnostic criteria: retrospective comparison using the BENEFIT clinical study dataset. Poster P648, ECTRIMS 2012.

