PAPER

Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes

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Background: The McDonald criteria include MRI evidence for dissemination in space and dissemination in time for the diagnosis of multiple sclerosis in young adult patients who present with clinically isolated syndromes (CIS) typical of the disease. Although a major advance, the criteria have limited sensitivity for making an early diagnosis.
Objective: To compare the performance of McDonald criteria and modified McDonald criteria for dissemination in space and time for assessing the development of clinically definite multiple sclerosis.
Methods: McDonald criteria were modified using the combination of a less stringent definition for dissemination in space and allowing a new T2 lesion per se after three months as evidence for dissemination in time. Modified and McDonald criteria were applied in 90 CIS patients at baseline and at three month follow up scans.
Results: Both criteria were highly specific (>90%) but the modified criteria were more sensitive (77% *v* 46%) and more accurate (86% *v* 73%).
Conclusions: These modified criteria should be evaluated in other CIS cohorts.

An essential requirement in making the diagnosis of multiple sclerosis is that there should be objective evidence for central nervous system (CNS) white matter lesions disseminated in both space and time. Past criteria relied mainly on clinical evidence for dissemination in space and time.[1] However, in 2001 new (McDonald) criteria were published that allowed MRI evidence for dissemination in space and time in the diagnosis of multiple sclerosis in patients who experienced a single acute clinical episode considered characteristic of the disease (known as a clinically isolated syndrome (CIS)).[2] While the McDonald criteria have high specificity for the subsequent development of clinically definite multiple sclerosis (CDMS) when applied in CIS cohorts followed prospectively,[3 4] they have several limitations.[5 6] Notably, the complex magnetic resonance imaging (MRI) criteria for dissemination in space [7 8] (table 1) have been considered too stringent, and the dissemination in time criterion of a new gadolinium enhancing lesion after three months has limited sensitivity in making an early diagnosis. The dissemination in space criteria also include gadolinium enhancement, which—strictly speaking—is a feature of lesion activity rather than location.

An early and accurate diagnosis of multiple sclerosis is increasingly important for counselling individual patients and potentially for making decisions on the use of disease modifying treatments. We were therefore interested in whether the MRI criteria for dissemination in space and dissemination in time could be modified so that they improve the accuracy of early diagnosis. In this report we describe the findings using the combination of a less stringent definition for dissemination in space and allowing a new T2 lesion per se after three months as evidence for dissemination in time.

METHODS

Rationale for modified criteria

Dissemination in space

The MRI criteria for dissemination in space were modified with the following aims:

- to retain the four anatomical regions that were included in the McDonald criteria, as they are considered characteristic for demyelination—that is, periventricular, juxtacortical, infratentorial, and spinal cord;
- to reduce to a minimum the number of lesions and regions needed for radiological dissemination in space—that is, there had to be at least one lesion in at least two of the four regions;
- to remove the option of including gadolinium enhancement as a feature of dissemination in space (that is, only T2 lesions and their location are considered).

The dissemination in space criteria were evaluated on the three month brain scans with and without the inclusion of baseline cord MRI findings. In cases of brain stem and spinal cord syndromes, all lesions within the symptomatic region were excluded.

Dissemination in time

The rationale for modifying the dissemination in time criteria was that in an earlier study of a subgroup of 56 patients from the currently reported cohort, we found that a new T2 lesion at a three month follow up was more sensitive but almost as specific as a gadolinium enhancing lesion (required by the McDonald criteria) for the development of CDMS.[9] Thus the modified dissemination in time criteria required one or more new T2 lesions at a three month follow up (a new lesion on the three month scan could also contribute to dissemination in space if situated in the regions specified by the criteria).

Patients

MRI acquisition protocols

The first MRI was done within three months of clinical onset (median 5.5 weeks, range 1 to 12), and consisted of a T2 weighted and gadolinium enhanced T1 weighted brain and

Abbreviations: CDMS, clinically definite multiple sclerosis; CIS, clinically isolated syndrome

Table 1 Performance of the McDonald and modified criteria* for clinically definite multiple sclerosis

	TP	FP	TN	FN	Sensitivity	Specificity	Accuracy
McDonald criteria for MS: brain MRI only	18	3	48	21	46%	94%	73%
McDonald criteria for MS: brain and cord MRI	18	3	48	21	46%	94%	73%
Modified criteria for MS: brain MRI only	29	4	47	10	74%	92%	84%
Modified criteria for MS: brain and cord MRI	30	4	47	9	77%	92%	86%
McDonald criteria for dissemination in space: brain MRI only	30	11	40	9	77%	78%	78%
McDonald criteria for dissemination in space: brain and cord MRI	31	11	40	8	79%	78%	79%
Modified criteria for dissemination in space: brain MRI only	35	13	38	4	90%	75%	81%
Modified criteria for dissemination in space: brain and cord MRI	37	15	36	2	95%	71%	81%
McDonald criteria for dissemination in time	19	5	46	20	49%	90%	72%
Modified criteria for dissemination in time	30	6	45	9	77%	88%	83%

*TP, true positive (criteria positive and CDMS); FP, false positive (criteria positive and not MS); TN, true negative (criteria negative and not MS); FN, false negative (criteria negative and CDMS); sensitivity, TP/(TP+FN); specificity, TN/(TN+FP); accuracy, (TP+TN)/(TP+FP+TN+FN).
McDonald criteria for dissemination in space
Three of the following four features: ⩾9 T2 brain lesions or ⩾1 gadolinium enhancing lesion; ⩾1 infratentorial lesions†; ⩾1 juxtacortical lesions; ⩾3 periventricular lesions (one spinal cord lesion can substitute for one brain lesion‡)
Modified criteria for dissemination in space
⩾1 T2 lesions in ⩾2 of the following regions: periventricular, juxtacortical, infratentorial†, spinal cord‡
†Excluded in cases of brain stem syndrome; ‡excluded in cases of spinal cord syndrome.
McDonald criteria for dissemination in time
⩾1 new gadolinium enhancing lesions.
Modified criteria for dissemination in time
⩾1 new T2 lesions.
CDMS, clinically definite multiple sclerosis; MRI, magnetic resonance imaging; MS, multiple sclerosis.

spinal cord scan (see Dalton *et al*, 2002[3] for protocol details). The second MRI was done approximately three months after the first (median 12 weeks, range 9 to 20), and consisted of a T2 weighted and gadolinium enhanced T1 weighted brain scan.

Both McDonald and modified criteria were applied to the scans, and their sensitivity, specificity, and overall accuracy for development of CDMS[1] was calculated as previously described.[3]

RESULTS

Thirty nine of the 90 patients (43%) developed CDMS as defined by the Poser criteria[1] during follow up, after a median of eight months from clinical onset (mean 14 months, range 2 to 48). The 51 patients (57%) who did not develop CDMS were followed up for a median of 39 months (mean 41, range 33 to 64). Both the McDonald and modified criteria had a high specificity for development of CDMS but the modified criteria were more sensitive and accurate (table 1).

Both dissemination in time criteria per se had high specificity for CDMS, but a new T2 lesion was considerably more sensitive than a new enhancing lesion. The dissemination in space criteria per se were less specific than the dissemination in time criteria. The modified criteria for multiple sclerosis had a higher specificity in the optic neuritis subgroup than in the non-optic-neuritis subgroup (95% *v* 83%; table 2).

The modified criteria had a high specificity for CDMS in the subgroups of patients whose first scan was done less than or more than six weeks from symptom onset (specificities 93% and 91%, respectively; table 3)

DISCUSSION

The modified MRI criteria for multiple sclerosis were more accurate than the McDonald criteria. This was because of an increased sensitivity of both the dissemination in space and dissemination in time components, while maintaining a high overall specificity. As well as improving the overall accuracy of diagnosing multiple sclerosis in patients with typical CIS, the modified criteria are also less complex than the existing criteria and should be easier to use. In not requiring gadolinium enhanced MRI, there are potential savings in time and cost.

High specificity is especially important in order to avoid diagnosing a disease when it is not present. It is notable that in both the McDonald and modified criteria the dissemination in time component was required to maintain a specificity greater than 90%. Both dissemination in space components alone were less specific, especially for the modified criteria; this should discourage making a diagnosis of multiple

Table 2 Performance of the McDonald and modified criteria*† in optic neuritis and non-optic neuritis subgroups

		TP	FP	TN	FN	Sensitivity	Specificity
Optic neuritis	McDonald criteria for MS	12	2	37	16	43%	95%
	Modified criteria for MS	20	2	37	8	71%	95%
Non-optic-neuritis	McDonald criteria for MS	6	1	11	5	55%	92%
	Modified criteria for MS	10	2	10	1	91%	83%

*TP, true positive (criteria positive and CDMS); FP, false positive (criteria positive and not MS); TN, true negative (criteria negative and not MS); FN, false negative (criteria negative and CDMS); sensitivity, TP/(TP+FN); specificity, TN/(TN+FP).
†Brain and spinal cord MRI findings are included, except that in patients with a brain stem or spinal cord syndrome, lesions in the symptomatic region (that is, infratentorial and spinal cord, respectively) were excluded.
CDMS, clinically definite multiple sclerosis; MRI, magnetic resonance imaging; MS, multiple sclerosis.

Table 3 Performance of the McDonald and modified criteria*† for clinically definite multiple sclerosis in subgroups first scanned less than or more than six weeks after CIS onset

		TP	FP	TN	FN	Sensitivity	Specificity
Patients scanned <6 weeks after CIS onset (n = 45)	McDonald criteria for MS	8	2	26	9	47%	93%
	Modified criteria for MS	13	2	26	4	76%	93%
Patients scanned >6 weeks after CIS onset (n = 45)	McDonald criteria for MS	10	1	22	12	45%	96%
	Modified criteria for MS	17	2	21	5	77%	91%

*TP, true positive (criteria positive and CDMS); FP, false positive (criteria positive and not MS); TN, true negative (criteria negative and not MS); FN, false negative (criteria negative and CDMS); sensitivity, TP/(TP+FN); specificity, TN/(TN+FP).
†Brain and spinal cord MRI findings are included, except that in patients with a brain stem or spinal cord syndrome, lesions in the symptomatic region (that is, infratentorial and spinal cord, respectively) were excluded.
CDMS, clinically definite multiple sclerosis; CIS, clinically isolated syndrome; MRI, magnetic resonance imaging; MS, multiple sclerosis.

sclerosis in CIS patients based solely on the findings of a single scan.

Although the present study was confined only to patients with a typical CIS, the lower specificity of MRI dissemination in space criteria per se—especially the modified criteria—suggests that if MRI is used to establish a diagnosis of multiple sclerosis, the MRI dissemination in time criteria should also be required in patients who have equivocal *clinical* evidence for dissemination in time (for example, a typical CIS plus another vaguely defined neurological episode).

High diagnostic specificity was obtained from brain MRI findings alone, and inclusion of spinal cord MRI findings increased the overall diagnostic accuracy of the modified criteria only slightly. While cord MRI is a primary investigation for spinal cord CIS, its role in patients with optic neuritis or brain stem syndromes appears more limited; it may be helpful, especially if brain MRI is abnormal but the dissemination in space criteria are not fulfilled. The similar outcomes for the subgroups first scanned more than or less than six weeks from symptom onset suggests that the exact timing of the first scan (within three months of symptom onset) is not crucial to the performance of the diagnostic criteria.

In order for MRI criteria to be applied reliably, several conditions should be met. First, the CIS should be unambiguously typical of those seen in multiple sclerosis—for example, unilateral optic neuritis, bilateral internuclear ophthalmoplegia, or partial myelopathy. Neither the McDonald nor these modified criteria have been tested in cohorts with clinically atypical or equivocal syndromes, nor have they been rigorously compared in established multiple sclerosis versus other white matter diseases. Furthermore, the non-optic-neuritis cohort in this study was small and other studies of larger non-optic-neuritis CIS cohorts are warranted. In some populations, the frequency of MRI abnormalities may differ between optic neuritis and non-optic-neuritis CIS,[10] and this may influence the performance of diagnostic criteria. Second, CIS diagnosis should be made by an experienced clinician, normally a neurologist or (in optic neuritis) a neuro-ophthalmologist. Third, the criteria should be applied only in younger adults (ages 16 to 50 years); in children, monophasic acute disseminated encephalomyelitis is more commonly seen, and in older adults non-specific MRI white matter lesions are often encountered. Fourth, the MRI should be of high quality, with careful attention to repositioning and consistency of image acquisition, and they should be interpreted by an experienced neuroradiologist. Finally, CSF examination for oligoclonal bands may still be a useful investigation, especially where clinical features are atypical; their value in combination with MRI criteria warrants further investigation in prospectively followed CIS cohorts.

A formal revision of McDonald criteria for multiple sclerosis is currently being undertaken by a new international panel and will need to consider carefully the extensive body of information that has emerged since the original criteria were published in 2001.[2] While the modifications used in the present study indicate potential areas for revision of the existing criteria in patients with CIS, it would be prudent for their performance to be evaluated further in other CIS cohorts, especially non- optic-neuritis cases.

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We report on 90 prospectively recruited CIS patients (38 men, 52 women; median age 32 years, range 17 to 50): 67 with optic neuritis (unilateral in 66, bilateral sequential in one), 15 with a brain stem syndrome, seven with a spinal cord syndrome, and one with an optic tract lesion. Patients were followed clinically until they developed CDMS, or for a mean of more than three years if they did not.
Written informed consent was obtained from all patients. The study was approved by the joint medical ethics committee of the Institute of Neurology and National Hospital for Neurology and Neurosurgery. The NMR Research Unit and the prospective follow up study of CIS subjects are supported by a programme grant from the MS Society of Great Britain and Northern Ireland which includes all scanning, image analysis, and clinical evaluation. We thank Drs Peter Brex and Jonathan O'Riordan for assisting with clinical recruitment and follow up; and David MacManus, Ros Gordon, and Chris Benton for undertaking the MRI.

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Competing interests: DHM has received grant support from Biogen Idec, Elan, Schering, and GlaxoSmithKline for performance of MRI analyses in clinical trials; honoraria for advisory or consultancy work, lectures, and related travel and accommodation expenses from Aventis, Biogen Idec, Bristol Myers Squibb, GlaxoSmithKline, Schering, Serono, UCB Pharma, and Wyeth. KF received salary support from Biogen Idec. CMD received salary support from Elan. GTP has received travel and accommodation expenses from Alcon. AJT has received honoraria for lecturing from Aventis and Schering. JS and KM have nothing to declare. The organisations mentioned in this conflict of interest statement did not participate in any aspect of the study design, execution, analysis, or write up.

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ECHO

Role of computed tomography before lumbar puncture: a survey of clinical practice

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Please visit the *Journal of Neurology, Neurosurgery, and Psychiatry* website [www.jnnp.com] for a link to the full text of this article.

Introduction: It is becoming increasingly common to request computed tomography (CT) to rule out space occupying lesions before lumbar puncture (LP), even in patients with no clinical signs. Imaging trends within a busy district general hospital in Oxfordshire, UK were analysed with results used to clarify when imaging should be considered mandatory.

Method: A retrospective six month sample was obtained comprising all adults considered for LP. Observed frequencies of abnormal examination findings compared with abnormal investigations were used to determine sensitivity, specificity, positive predictive, and negative predictive values to assess the validity of using a normal clinical examination as a basis for excluding CT.

Results: 64 patients were considered for LP. In total, 58 patients underwent LP, with a single patient receiving two. After an abnormal CT scan, six patients did not undergo a planned LP. In all six of these cases subarachnoid haemorrhage was detected, and in all cases this was considered a probable diagnosis. In no case was an LP precluded by an unsuspected space occupying lesion. Neurological examination showed a sensitivity of 0.72 (0.52 to 0.93), specificity 0.78 (0.64 to 0.91), positive predictive value 0.61 (0.41 to 0.83), and negative predictive value 0.85 (0.73 to 0.97).

Discussion: The high sensitivity and negative predictive values support normal neurological examination as an effective predictor of normal CT scan. This permits the recommendation in cases where subarachnoid haemorrhage is not suspected, a CT scan can be avoided provided there are no abnormal findings on physical or fundoscopic examination.

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