Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald Criteria"

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New diagnostic criteria for multiple sclerosis integrating magnetic resonance image assessment with clinical and other paraclinical methods were introduced in 2001. The "McDonald Criteria" have been extensively assessed and used since 2001. New evidence and consensus now strengthen the role of these criteria in the multiple sclerosis diagnostic workup to demonstrate dissemination of lesions in time, to clarify the use of spinal cord lesions, and to simplify diagnosis of primary progressive disease. The 2005 Revisions to the McDonald Diagnostic Criteria for MS should simplify and speed diagnosis, whereas maintaining adequate sensitivity and specificity.

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In 2001, the International Panel on the Diagnosis of Multiple Sclerosis presented new diagnostic criteria for multiple sclerosis (MS) that have come to be known as the "McDonald Criteria" after the chair of that group, Dr W. Ian McDonald.[1] The Criteria became known internationally,[2] and they were rapidly adopted by the MS community.

The intent of the McDonald Criteria was to present a diagnostic scheme that could be used by the practicing neurologist to better and more reliably diagnosis MS, balancing early diagnosis with the need to avoid false-positive diagnosis. The Criteria formally incorporated magnetic resonance imaging (MRI) into the well-established diagnostic workup that focuses on detailed neurological history and examination and a variety of paraclinical laboratory examinations. Components of the Criteria were evidence based wherever possible, and the International Panel stated their limitations and encouraged prospective clinical testing to evaluate their utility and validity.

In the years since their original presentation, several publications have appeared that have largely supported the utility of the Criteria: Retrospective analyses of extant datasets have shown that the Criteria could reliably signal the development of clinically definite MS earlier than prior criteria, and that they had a reasonably high level of specificity and sensitivity compared with prior criteria.[3–6] Additional published studies have explored potential modifications of the original Criteria with particular emphasis on determining dissemination of lesions in time and space (the core concept in MS diagnosis), incorporating different types of imaging criteria into the diagnostic scheme, and assessing the value of cerebrospinal fluid (CSF) analysis, particularly for diagnosis of primary progressive multiple sclerosis (PPMS).[7–11] Other studies and comments from the MS clinical community that were solicited by the International Panel[12] before a meeting in March 2005 questioned the value of the original Criteria in populations other than adults of Western European ethnic origins and pointed to aspects of the original Criteria that were considered to be vague, confusing, or that required additional explanation and guidance to be optimally useful.

The International Panel reconvened in March 2005 in Amsterdam, nearly 5 years after the original Panel convened in London, to review progress since the original Criteria were developed, to evaluate whether the

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global framework of the Criteria continued to be appropriate, and to recommend appropriate revisions to the original Criteria. The goals of these revisions are to incorporate new evidence where available, to develop refined consensus where evidence from research studies is scant, and to simplify and clarify original definitions and concepts that users have thought were confusing or difficult to implement. The resulting consensus developed by the International Panel is presented here as the 2005 Revisions to the McDonald Criteria.

Considerations Related to the Original Criteria

General Considerations

The International Panel evaluated all available published research relating to the original Criteria and input provided from the MS clinical community and determined that the Criteria provided reasonably good utility for "classical" MS seen in a typical adult Caucasian population of Western European ethnic origin. Data that have been collected to date, largely from retrospective datasets in research-focused MS clinical centers, suggest that the Criteria, although imperfect, provide a good mix of specificity and sensitivity to allow for an early diagnosis of MS. It is less clear how adequate the Criteria are in a general neurology practice setting or for determining if an alternative diagnosis might exist in patients who present with a "clinically isolated syndrome" of inflammatory demyelinating disease and who fulfill the Criteria for definite MS, but may, in fact, have a different condition.[3,6,9]

The Criteria have not been adequately tested in populations other than those representing classical MS in Western adult populations. In preliminary case series studies of pediatric-onset MS, different disease characteristics may make the original Criteria less sensitive.[13] In Asians, recurrent, demyelinating diseases with clinical characteristics that overlap with Western MS, such as optic-spinal forms of MS, may be indistinguishable from neuromyelitis optica (NMO; Devic's disease) and recurrent transverse myelitis. The Asian neurological community is focusing on diagnosis and related issues of prognosis and treatment in the populations they serve, to determine whether the Criteria can be generalized, and if not, to determine how modifications to the Criteria will make them more appropriate for such populations (B. Weinshenker, personal communication). Similar efforts are ongoing in Latin America.

Clinical Considerations

The McDonald Criteria appear to have been incorrectly interpreted by some as mainly relying on MRI for making a diagnosis of MS. In fact, the McDonald Criteria cannot even be applied without careful clinical evaluation of the patient. Classification of presenting symptoms and signs as either monofocal (indicative of a single lesion) or multifocal (indicative of more than one lesion) is fundamental to the concept of dissemination in space and time, which are the core requirements of diagnosis. A purely clinical diagnosis remains appropriate when MRI and other paraclinical examinations are not possible, and a standardized approach to the interpretation of clinical symptoms and signs in patients with clinically isolated syndrome in the context of a clinical trial was published recently.[14]

Typically, a diagnostic workup for MS is performed in patients who present with initial symptoms "characteristic of MS" or with "unusual presentations" that might be MS, as Paty and colleagues[15] have described carefully. Diagnosis is more problematic when a patient presents with a "clinically vague syndrome" for which the examining physician cannot document an objective clinical lesion at onset and where one relies on patient reporting of past clinical symptoms that might suggest MS. The original McDonald Criteria noted that suspicious symptoms could trigger the search for objective findings that can lead to an MS diagnosis, but that objective findings were required to make the diagnosis. There was some sympathy among International Panel members to allow selected symptoms that are clearly and specifically enunciated by the patient (eg, Lhermitte's symptom, trigeminal neuralgia, numbness ascending to the waist or higher, and so forth) coupled with objective paraclinical findings to be sufficient as an indicator of a prior or current attack needed for an MS diagnosis. However, the majority of the group was reluctant to endorse the diagnosis of MS in the absence of any objective clinical findings, even if objective paraclinical findings are in place, at least until such a scheme is tested in prospective settings.

Diagnosis of MS requires the elimination of alternative conditions that might "mimic" the disease. The Panel discussed differential diagnosis of nondemyelinating diseases and the emerging spectrum of "idiopathic inflammatory demyelinating diseases."[16] These may present with characteristics that fulfill current diagnostic criteria for MS, but they might be better considered as separate entities because of differences in their genetic background, pathophysiology, prognosis, and treatment. For example, whether acute and recurrent disseminated encephalomyelitis exist as separate entities from MS is unclear. NMO sometimes is mistaken for MS, and recurrent optic neuritis and transverse myelitis might be limited forms of NMO.[17,18] Recent advances in the development of serum antibody markers specific to NMO[19] may aid in such differential diagnoses. It may be of value, as a separate undertaking, to develop a set of "minimal assessments" related to differential diagnoses for MS, particularly those presenting as idiopathic inflammatory demyelinating diseases.

Magnetic Resonance Imaging Considerations

The MRI requirements in the original McDonald Criteria were stringent, and some might say "conservative," in their reliance on the Barkhof[20] imaging criteria as modified by Tintoré and coworkers[21] to determine whether MRI findings satisfy criteria for dissemination in time and space. Others have proposed more liberal use of imaging criteria to determine dissemination in *space*.[9] The Panel accepts that MS *may* be the correct diagnosis with less stringent imaging criteria, but it was uncomfortable making changes that would allow MRI confirmation of dissemination in space based on lower stringency imaging criteria without appropriate prospective data. Most studies performed so far have been inadequately designed to directly address this issue.[22] Furthermore, new imaging technologies are constantly developing that will aid in diagnosis. Priority should be given to visualization of intracortical lesions, use of higher field strength, and analysis of "normal appearing brain tissue,"[23] because preliminary evidence suggests that "occult" damage in normal-appearing white and gray matter seen with magnetization transfer, diffusion tensor imaging, or spectroscopy is an early feature of MS, whereas it may not occur in other demyelinating conditions such as acute disseminated encephalomyelitis and NMO.[24]

However, the Panel does recommend some changes in the use and interpretation of imaging criteria for dissemination in *time* in its 2005 revisions and provides clearer guidance on incorporating spinal cord lesions into imaging criteria (see later). These changes are based largely on the consensus that both dissemination in time and space remain an essential core of MS diagnosis but that, in a hierarchical fashion, rigorous demonstration of dissemination in time might be more important than dissemination in space.

Cerebrospinal Fluid Considerations

The incorporation of CSF findings into the McDonald Criteria has been supported by studies that suggest that CSF analysis increases diagnostic sensitivity, though perhaps at the cost of specificity and accuracy.[6,25] However, findings in one large study of PPMS[11] have lead to a recommendation by the Panel to revise the CSF criteria for this population of patients, and it is no longer a requirement for diagnosis (see later).

Specific Recommendations to Modify the McDonald Criteria: The 2005 Revisions

The following sections discuss in detail specific recommendations for the 2005 revisions to the McDonald Criteria.

Magnetic Resonance Imaging Criteria for Dissemination of Lesions in Time

Data gathered since the original dissemination of the McDonald Criteria in 2001 support the role of T2 lesions, not just contrast-enhancing lesions, for demonstrating dissemination in time in a less restrictive way than allowed in the original criteria.[7,26] Although Dalton and colleagues[7] demonstrated that a new T2 lesion at 3 months is a reliable marker of dissemination in time, there was a median of 5 weeks from onset of symptoms to the baseline MRI scan in their studies. The Panel believed that T2 lesions can be useful for demonstrating dissemination in time more rapidly than over the 3-month period required in the original McDonald Criteria, but it agreed that T2 lesions occurring in the first few weeks after the onset of a first clinical episode should *not* be considered a separate, new event. In keeping with the definition that clinical relapses must be separated by 1 month, it was agreed that new T2 lesions on MRI should occur at least 1 month after disease onset, close to the median time in the work by Dalton and colleagues.[7] Practically, this means that any new T2 lesion occurring at any time point after a so-called reference scan performed at least 30 days after the onset of the initial clinical event is useful in meeting imaging diagnostic criteria for dissemination in time. This revision will simplify and clarify the prior Criteria, allow for a more rapid diagnosis, and provide more flexibility in imaging criteria, whereas still providing unequivocal proof of dissemination in time (Table 1).

Although recommending these streamlined criteria, the International Panel cautions that determination that a T2 lesion is indeed new can be challenging. A new T2 lesion must be of sufficient size and location to reflect one that could not have been missed previously for technical reasons of slice orientation, thickness or spacing, tissue contrast, patient motion, or other artifacts. This requires standardized scanning procedures with emphasis on careful repositioning, as well as input from qualified evaluators experienced in MS imaging.[27,28]

Incorporation of Spinal Cord Lesions into the Imaging Requirements

The original McDonald Criteria set out specific criteria that needed to be fulfilled, based largely on brain MRI scan outcomes, to demonstrate diagnostically relevant brain abnormality. These criteria, from work of Barkhof and colleagues[20] as modified by Tintoré and coworkers,[21] include evidence of three of the following four outcomes: one gadolinium-enhancing lesion or nine T2-hyperintense lesions if there is no gadolinium-enhancing lesion, at least one infratentorial lesion, at least one juxtacortical lesion, or at least three periventricular lesions (Table 2). As noted, the Panel con-

Table 1. Magnetic Resonance Imaging Criteria to Demonstrate Dissemination of Lesions in Time

Original McDonald Criterion	2005 Revisions
1. If a first scan occurs 3 months or more after the onset of the clinical event, the presence of a gadolinium-enhancing lesion is sufficient to demonstrate dissemination in time, provided that it is not at the site implicated in the original clinical event. If there is no enhancing lesion at this time, a follow-up scan is required. The timing of this follow-up scan is not crucial, but 3 months is recommended. A new T2- or gadolinium-enhancing lesion at this time then fulfills the criterion for dissemination in time. 2. If the first scan is performed less than 3 months after the onset of the clinical event, a second scan done 3 months or longer after the clinical event showing a new gadolinium-enhancing lesion provides sufficient evidence for dissemination in time. However, if no enhancing lesion is seen at this second scan, a further scan not less than 3 months after the first scan that shows a new T2 lesion or an enhancing lesion will suffice.	1. There are two ways to show dissemination in time using imaging: a. Detection of gadolinium enhancement at least 3 months after the onset of the initial clinical event, if not at the site corresponding to the initial event b. Detection of a *new* T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event

cluded that although it is biologically plausible to liberalize these requirements for a "positive" MRI indicating MS-like brain abnormality, lack of prospective data to test the specificity and sensitivity of any such liberalized criteria make it unwise at this point to change these criteria.

It was recommended in the original McDonald Criteria that "one spinal cord lesion can be substituted for one brain lesion," a statement that in retrospect has been confusing and provides insufficient guidance for use of spinal cord imaging in the diagnostic workup.[29] At its Amsterdam meeting, the International Panel reached consensus on the following revisions and guidance related to spinal cord lesions:

1. Spinal cord imaging can be extremely helpful in the workup for the important step of excluding alternative diagnoses. Whereas lesions in the brain can develop in healthy aging people, this is not typical in the spinal cord.[30–32]
2. Spinal cord imaging that detects MS-typical lesions (little or no swelling of the cord; unequivocally hyperintense if detected with T2-weighted imaging; at least 3 mm in size, but less than 2 vertebral segments in length; and occupying only part of the cord cross section) is particularly helpful if brain imaging does not detect dissemination in space in a patient suspected to have MS.[8,10,33]
3. For dissemination in space, a spinal cord lesion is equivalent to, and can substitute for, a brain infratentorial lesion, but *not* for a periventricular or juxtacortical lesion; an enhancing spinal cord lesion is equivalent to an enhancing brain lesion, and an enhancing spinal cord lesion can "count" doubly in fulfilling the criteria (eg, a single enhancing spinal cord lesion can "count" for an enhancing lesion *and* an infratentorial lesion); and individual spinal cord lesions can contribute together with individual brain lesions to reach the

Table 2. Magnetic Resonance Imaging Criteria to Demonstrate Brain Abnormality and Demonstration of Dissemination in Space

Original McDonald Criteria	2005 Revisions
Three of the following: 1. At least one gadolinium-enhancing lesion or nine T2 hyperintense lesions if there is no gadolinium-enhancing lesion 2. At least one infratentorial lesion 3. At least one juxtacortical lesion 4. At least three periventricular lesions	Three of the following: 1. At least one gadolinium-enhancing lesion or nine T2 hyperintense lesions if there is no gadolinium enhancing lesion 2. At least one infratentorial lesion 3. At least one juxtacortical lesion 4. At least three periventricular lesions
NOTE: One spinal cord lesion can substitute for one brain lesion/	NOTE: A spinal cord lesion can be considered equivalent to a brain infratentorial lesion: an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions.

Based on data from Barkhof and colleagues[20] and Tintoré and coworkers.[21]

required nine T2 lesions to satisfy Barkhof criteria as modified by Tintoré (see Table 2).

4. Spinal cord lesions should be focal (ie, clearly delineated and circumscribed as seen on heavily T2-weighted images) in nature for consideration in MS diagnosis. Although diffuse cord changes occur in MS, especially in (primary) progressive MS, these changes are not sufficiently reliable to allow for their incorporation into the diagnostic criteria.
5. Finally, repeat spinal cord imaging in patients without symptomatic myelitis has a low yield in efforts to demonstrate dissemination of lesions in time.[8] Therefore, repeat cord imaging is recommended only to support an MS diagnosis when there is a clinical reason to suspect a new cord lesion.

Making a Diagnosis of Primary Progressive Multiple Sclerosis

Establishing a diagnosis of PPMS continues to be problematic. The original McDonald Criteria as they applied to PPMS were based on the work of Thompson and colleagues,[34] which provided criteria derived for rigorous research purposes rather than a nonresearch clinical setting.

The 2005 Revisions provide simplified criteria for diagnosis of PPMS, take advantage of new research that shows that PPMS can be diagnosed reliably in the absence of positive CSF findings (at least in the presence of typical brain MRI changes),[11] and provides a more detailed description of brain and spinal cord pathology as seen on MRI.[35] The Panel continues to believe that a positive CSF finding (preferably based on isoelectric focusing evidence of oligoclonal IgG bands with immunofixation demonstrating that bands that are different from those in serum or an increased IgG index, or both)[36–38] increases the "comfort level" for a diagnosis of MS in individuals with insidious progression of disease from onset. However, such CSF findings are not specific and may be commonly detected in patients with progressive myelopathies of other causes, particularly those associated with infection (eg, retrovirus). Depending on the strength of other diagnostic criteria, a positive CSF finding is no longer a requirement for diagnosis of PPMS (Table 3).

These Revised Criteria for diagnosing MS in a patient with a progressive-from-onset disease course stress clinical and imaging (brain or spinal cord) evidence for diagnosis and place less emphasis on CSF findings. The Panel recognizes that in proposing such liberalized criteria, prospective testing for specificity and sensitivity will be required.

Conclusions

The 2005 Revisions of the MS diagnostic criteria (Table 4) retain the core features of the original McDonald Criteria: emphasis on objective clinical findings, dependence on evidence of dissemination of lesions in time and space, use of supportive and confirmatory paraclinical examination to speed the process and to help eliminate false-negative and -positive diagnoses, focus on specificity rather than sensitivity, and need to eliminate better explanations for the diagnosis. The main goals here are to incorporate evidence-based data obtained since the publication of the McDonald Criteria, to present revised consensus, and to simplify and clarify issues that have caused confusion and misinterpretation. These Revised Criteria, in particular the "liberalized" requirements for imaging and CSF findings, are major changes that are likely to have an impact on neurological practice.

The Revised Criteria are, as far as possible, data driven. The 2005 Revisions will benefit from truly prospective testing in a typical neurology practice setting to confirm their value and to inform future revisions. This will be particularly important to assess criteria for

Table 3. Diagnosis of Multiple Sclerosis in Disease with Progression from Onset

Original McDonald Criteria	2005 Revisions
1. Positive CSF *and* 2. Dissemination in *space* by MRI evidence of nine or more T2 brain lesions *or* Two or more cord lesions *or* Four to eight brain lesions and one cord lesion *or* Positive VEP with four to eight MRI lesions *or* Positive VEP with less than four brain lesions plus one cord lesion *and* 3. Dissemination in *time* by MRI *or* Continued progression for 1 year	1. One year of disease progression (retrospectively or prospectively determined) 2. *Plus* two of the following: a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) b. Positive spinal cord MRI (two focal T2 lesions) c. Positive CSF[a] (isoelectric focusing evidence of oligoclonal IgG bands or increased IgG index, or both).

[a]MRI demonstration of space dissemination must fulfill the criteria derived from Barkhof and colleagues[20] and Tintoré and coworkers[21] as presented in Table 2.

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; VEP = visual-evoked potential.

Table 4. The 2005 Revisions to the McDonald Diagnostic Criteria for Multiple Sclerosis

Clinical Presentation	Additional Data Needed for MS Diagnosis
Two or more attacks[a]; objective clinical evidence of two or more lesions	None[b]
Two or more attacks[a]; objective clinical evidence of one lesion	Dissemination in space, demonstrated by: ● MRI[c] *or* ● Two or more MRI-detected lesions consistent with MS plus positive CSF[d] *or* ● Await further clinical attack[a] implicating a different site
One attack[a]; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by: ● MRI[e] *or* ● Second clinical attack[a]
One attack[a]; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by: ● MRI[c] *or* ● Two or more MRI-detected lesions consistent with MS plus positive CSF[d] *and* Dissemination in time, demonstrated by: ● MRI[e] *or* ● Second clinical attack[a]
Insidious neurological progression suggestive of MS	One year of disease progression (retrospectively or prospectively determined) *and* Two of the following: a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP)[f] b. Positive spinal cord MRI (two focal T2 lesions) c. Positive CSF[d]

If criteria indicated are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS; if suspicious, but the criteria are not completely met, the diagnosis is "possible MS"; if another diagnosis arises during the evaluation that better explains the entire clinical presentation, then the diagnosis is "not MS."

[a]An attack is defined as an episode of neurological disturbance for which causative lesions are likely to be inflammatory and demyelinating in nature. There should be subjective report (backed up by objective findings) or objective observation that the event lasts for at least 24 hours.[1]

[b]No additional tests are required; however, if tests (MRI, CSF) are undertaken and are *negative,* extreme caution needs to be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture and some objective evidence to support a diagnosis of MS.

[c]MRI demonstration of space dissemination must fulfill the criteria derived from Barkhof and colleagues[20] and Tintoré and coworkers[21] as presented in Table 2.

[d]Positive CSF determined by oligoclonal bands detected by established methods (isoelectric focusing) different from any such bands in serum, or by an increased IgG index.[36–38]

[e]MRI demonstration of time dissemination must fulfill the criteria in Table 1.

[f]Abnormal VEP of the type seen in MS.[39,40]

MS = multiple sclerosis; MRI = magnetic resonance imaging; CSF = cerebrospinal fluid; VEP = visual-evoked potential.

diagnosing PPMS, to obtain data to further refine and perhaps liberalize the still rather complex requirements for imaging outcomes, and to incorporate and test newer imaging technologies as they develop.

To this end, there is a need for motivated investigators working together in environments that support multicenter, institutionalized, prospective follow-up for clinical assessment and screening in large populations. Such efforts will be enhanced by creating registries, perhaps Internet based, and by focusing especially on identified population cohort studies to help define the value of these criteria in groups of patients for whom they have not been adequately explored.

The Panel recognizes that both the original McDonald Criteria and the 2005 Revisions are most applicable in settings where paraclinical examinations (imaging, CSF analysis, and so forth) are readily (and rapidly) available after initial disease onset and where equipment, analysis, and interpretation are standardized and reliable. In the absence of such facilities, however, a diagnosis of MS can still be made reliably using solely clinical criteria in the hands of a knowledgeable physician.

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