Early Identification of Clinically Isolated Syndrome – How this is Best Achieved and the Implications for Patient Outcomes

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Abstract
Magnetic resonance imaging (MRI) evidence for dissemination in space (DIS) and dissemination in time (DIT) are used within the McDonald criteria for the diagnosis of multiple sclerosis (MS). These criteria are complex and in some patients several MRI examinations are needed to achieve an accurate diagnosis. In order to make an earlier diagnosis of clinically definite multiple sclerosis (CDMS) in patients with clinically isolated syndromes (CIS), new criteria have been proposed in which DIS and DIT requirements are simpler, maximising sensitivity and conserving specificity. These data have led to a new proposal of MRI criteria for MS diagnosis. The historical evolution of MS criteria and the new evidence are reviewed in this article.

Keywords
Clinically isolated syndrome, clinically definite multiple sclerosis, magnetic resonance imaging, diagnostic criteria, dissemination in time, dissemination in space

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) that mainly affects young adults and is characterised by an inflammatory demyelination of different areas of the CNS occurring at different time points. MS has several forms of presentation, including episodic subacute periods of worsening (the most common, initially), gradual progressive deterioration of neurological function or a combination of both. These different presentations have been given standardised names – relapsing–remitting (RR), secondary progressive, primary progressive and progressive-relapsing – describing the clinical phenotype of the disease.

Unfortunately reliable biomarkers that enable the prediction of the clinical course of MS from the beginning of the disease are yet to be identified. Approximately 85% of patients start out with RRMS and the presentation, despite the possibility of having multifocal signs and symptoms, is frequently monosymptomatic. Patients often present with unilateral optic neuritis, a brainstem syndrome or partial myelitis, which are the more common initial symptoms in MS. These presentations are known as clinically isolated syndromes (CIS).

In recent years, changes in MS diagnostic criteria have been proposed, mainly due to the incorporation of updated magnetic resonance imaging (MRI) criteria[1,2] and new data from trials incorporating these criteria have now been published.[3–5] In a long-term follow-up study, Beck et al.[6] and Fisniku et al.[7] showed that clinically-definite MS (CDMS) developed in 56–82% of patients with abnormal MRI and in approximately 20% with normal MRI at

presentation. As no single clinical feature or diagnostic test is sufficient for MS diagnosis, criteria have been developed and modified combining different clinical, biological and radiological information. These criteria essentially focus on the demonstration of the more relevant aspects of disease course – the dissemination of lesions in space (DIS) and the dissemination of lesions in time (DIT) – and the exclusion of alternative causes that can mimic MS.[8,9]

Why is Early Diagnosis Important?
The efficacy of interferon-beta in RRMS patients has been clearly demonstrated. Results from a follow-up study on patients who participated in the pivotal beta-1b interferon trial showed the benefit of early treatment. The disability, mortality and MRI scores of patients from the treated group were better than the placebo-group patients treated in the extension phase of the study.[10] Similar results were obtained from the pivotal glatiramer acetate trial. Here, a significantly lower proportion of patients from the placebo group treated with glatiramer acetate during the extension phase were neurologically stabilised or improved compared with patients who had been treated with glatiramer acetate from the start of the trial.[11]

Phase III clinical trials (the Controlled High-Risk Subjects Avonex® Multiple Sclerosis Prevention Study [CHAMPS], the Early Treatment Of Multiple Sclerosis [ETOMS] study, the Betaferon®/Betaseron® in Newly Emerging Multiple Sclerosis for Initial Treatment [BENEFIT] trial and the Study to Evaluate Early Glatiramer Acetate Treatment in Delaying Conversion to CDMS of Subjects Presenting With CIS

[PreCISe]) in patients with isolated neurological episodes and MRI suggestive of MS have demonstrated the usefulness of immunomodulatory therapy in delaying the occurrence of a second relapse.[12–15] As a result of the evidence from these studies, immunomodulatory therapy is now approved for use in MS from the very first relapse. All immunomodulatory drugs have demonstrated their usefulness compared with placebo in different stages of the disease, with the efficacy proving to be better the earlier therapy is started. An early diagnosis of MS is therefore important for counselling individual patients and making decisions on the use of evidence-based disease-modifying treatments.

The Development of Criteria for the Diagnosis of Multiple Sclerosis

The diagnosis of MS is currently based on clinical parameters such as medical history and neurological examination, and paraclinical measures such as MRI, cerebrospinal fluid (CSF) examination and evoked potential testing.

Poser Diagnostic Criteria

Traditionally, diagnostic criteria for MS stated that a diagnosis of CDMS required clinical evidence of two or more lesions on at least two occasions.[16] In 1983, these criteria were expanded by Poser et al. to include the use of paraclinical parameters such as evoked potentials and CSF findings.[17] Poser et al. defined diagnostic categories and the highest degree of confidence was for CDMS, which was achieved when two relapses were identified, each confirmed by clinical examination, separated in space and time. However, these criteria anteced MRI and thus did not give specific recommendations on how to use this (now) important paraclinical tool.

The Impact of the Introduction of Magnetic Resonance Imaging

MRI has been shown to be the single most informative diagnostic procedure in recent years. Areas of abnormality on T2-weighted or proton-density-weighted images in a pattern highly characteristic for MS occur in more than 95% of patients with clinically definite disease and in 50–70% of patients with a CIS. MRI is also a powerful method for excluding other diseases that might simulate MS, which is a critical additional diagnostic step.

Based on developments on MRI techniques, in 1988 Paty et al.[18] proposed criteria for MS diagnosis that were supported by the presence of four or more lesions or three lesions, one of which needed to be periventricular. These criteria were prospectively evaluated in CIS patients and showed high sensitivity, but relatively low specificity, for the development of CDMS. Later, Fazekas et al.[19] proposed a modification of the MRI criteria. This consisted of the consideration of three or more lesions with at least two of the following characteristics:

- periventricular;
- infratentorial; and
- larger than 6mm.

These criteria showed both high sensitivity and specificity for MS diagnosis[20] when retrospectively evaluated in established MS and other disorders. However, when applied prospectively in CIS patients their performance was inferior in predicting conversion to CDMS.[21]

The Barkhof–Tintoré Criteria

In 1997 Barkhof et al.[22] proposed a model of four parameters that predicted conversion to CDMS better than previous or existing models. Those parameters were the presence of the following types of lesions:

- ≥1 gadolinium-enhancing;
- ≥1 juxtacortical;
- ≥1 infratentorial; and
- ≥3 periventricular.

The Barkhof criteria were further modified by Tintoré et al.[23] They allowed the gadolinium-enhancing lesion to be replaced by nine T2 lesions and introduced the concept of having at least three of the four Barkhof parameters. This enabled Tintoré et al. to achieve a higher accuracy and better balance between sensitivity and specificity for predicting CIS conversion to CDMS.

The McDonald Criteria

In 2001, an international panel published new guidelines for the diagnosis of MS. As with the Poser criteria, these relied on objective evidence of dissemination in time and space. These criteria (commonly referred to as the McDonald criteria[1] in recognition of the panel's chair, W Ian McDonald), included MRI evidence to support DIS and DIT. These criteria represented the first constructive effort to address how to use non-invasive observations in conjunction with clinical findings. The MRI DIS criteria chosen by the panel were those proposed by Barkhof et al.[22] and Tintoré et al.,[23] with the addition that a spinal cord lesion could substitute a brain lesion.

An alternative criterion introduced for DIS consisted of the presence of at least two MRI lesions plus positive CSF (i.e. the presence of oligoclonal bands or an elevated immunoglobulin G index). To support the evidence for DIT, these criteria require a gadolinium-enhancing lesion on a MRI scan obtained at least three months after CIS onset and in a separate location from the initial clinical event or a new T2 lesion on a scan subsequent to a reference one obtained at least three months after CIS onset. When retrospectively applied to CIS cohorts, the 2001 McDonald criteria showed high specificity for CDMS, but limited sensitivity.[24,25]

The Updated McDonald Criteria

The international panel re-convened in 2005 to review progress since the original criteria were published, evaluate whether the global framework of the criteria continued to be appropriate and determine whether any kind of revision should be recommended. In fact, changes in the 2001 criteria were proposed[2] in order to simplify and clarify issues that had caused some difficulty and misinterpretation, particularly concerning imaging and CSF findings. With respect to DIT demonstration, two new ways of detecting MS have replaced those previously used:

- detection of a gadolinium-enhancing lesion at least three months after CIS onset if not at the site corresponding to the initial event; and
- detection of a new T2 lesion appearing at any time compared with a reference scan taken at least 30 days after the onset of the initial clinical event.

For DIS, the role of spinal cord lesions has been redefined:

Table 1: Performance of the Different Magnetic Resonance Imaging Criteria for Predicting Conversion to Clinically Definite Multiple Sclerosis

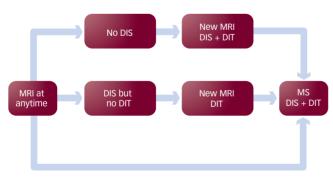| DIS and DIT criteria	Sensitivity (95% CI) %	Specificity (95% CI) %
McDonald (2001)	47.1 (36–58)	91.1 (85–95)
McDonald (2005)	60 (49–70)	87.8 (81–93)
Swanton (2005)	71.8 (61–81)	87 (80–92)
Rovira (2009)	45.2 (31–60)	86.6 (81–91)

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

Table 2: Former and New Magnetic Resonance Imaging Criteria for Dissemination in Space and Time for Multiple Sclerosis

	McDonald (2005)	MAGNIMS (2010)
DIS	≥3 of: ≥9 T2 lesions or ≥1 Gd-enhancing lesion ≥3 PV lesions ≥1 JC lesions ≥1 PF or SC lesion Spinal cord lesions can be included in total lesion count Presence of ≥2 T2 lesions plus CSF OCB are considered as DIS	≥1 lesion in each of the following characteristic locations: PV JC PF SC All lesions in symptomatic regions are to be excluded in BS and SC syndromes CSF findings are yet to be considered
DIT	1) ≥1 Gd-enhancing lesion at least 3 months after CIS onset 2) A new T2 lesion with reference to a baseline scan obtained at least 30 days after CIS onset	1) Simultaneous presence of asymptomatic Gd-enhancing and non-enhancing lesions at any time 2) A new T2 lesion and/or Gd-enhancing lesion on follow-up MRI irrespective of timing of baseline scan

BS = brainstem; CIS = clinically isolated syndrome; CSF = cerebrospinal fluid; DIS = dissemination in space; DIT = dissemination in time; Gd = gadolinium; JC = juxtacortical; OCB = oligoclonal bands; PF = posterior fossa; PV = periventricular; SC = spinal cord.

Figure 1: Diagnostic Algorithm in Patients with Typical Clinically Isolated Syndromes

Dissemination in space (DIS) and time (DIT) are referred to in Table 2 (Magnetic Imaging in Multiple Sclerosis [MAGNIMS] proposal). MRI = magnetic resonance imaging.

- a cord lesion is equivalent to, and can be a substitute for, a brain infratentorial lesion, but not for a periventricular or juxtacortical lesion;
- an enhancing cord lesion can doubly fulfill the criteria; and
- individual spinal cord lesions can contribute along with individual brain lesions to reach the required nine T2 lesions to satisfy the Barkhof et al.[22] criteria, as modified by Tintoré et al.[23]

The 2005 and 2001 McDonald criteria were recently compared and the revised criteria showed an increase in sensitivity (60 *versus* 47%) while retaining a good specificity (88 versus 91%).[3] The 2005 revision maintains the core features of the original McDonald criteria:

- emphasis on objective clinical findings;
- the need for evidence of dissemination of lesions in space and time; and
- the use of supportive paraclinical tools to speed up the process of diagnosis and help to eliminate false-positive and false-negative results.

Recent Proposals for New Magnetic Resonance Imaging Diagnostic Criteria

There have been several proposals for new MS criteria, as the McDonald criteria are very stringent and complex. Although highly specific, the MRI DIS (Barkhof–Tintoré) criteria have been considered too stringent. The Barkhof–Tintoré criteria were not strictly defined as DIS criteria, as neither of the studies in which they were tested actually addresses the question of spatial dissemination, but the ability of just one MRI scan to predict CDMS.[22,23] Gadolinium enhancement is currently considered for both DIS and DIT criteria; however, gadolinium-enhancing lesions are more a feature of lesion activity than a DIS characteristic.

DIT criteria are also complex, necessary requiring at least two MRI scans obtained in the first month after the first episode, so scans performed within the first 30 days of symptom onset cannot be used as a reference for DIT. Since in practice most patients have their first scan within the first month (many patients within the first week) of the onset of CIS symptoms, it would be an advantage to allow this scan to be the reference scan for determining DIT.

It is interesting to note that Poser criteria allowed a very early and simple diagnosis of MS following the first MS relapse if there was either clinical evidence of two separate lesions and CSF abnormalities; or clinical evidence of one lesion, paraclinical evidence of another separate lesion and CSF abnormalities (laboratory-supported definite MS).[17]

Some authors have highlighted the need for high-specificity MRI criteria, since MS can be over-represented when it is suspected but not clinically confirmed.[26] With this, it is interesting to develop new, simpler, user-friendly DIS and DIT criteria that improve the accuracy of early diagnosis.

In 2003, the American Academy of Neurology recommended a simpler criterion – the presence of at least three T2 lesions[27] – but this proved to have a very low specificity compared with the Barkhof criteria,[28] so false-positive results and overdiagnosis of MS could be a risk.

In 2005, the Queen Square group led the proposal of new imaging criteria for MS diagnosis, both for DIS and DIT.[29] DIS criteria retained the four anatomical regions that were included in the McDonald criteria as they are considered characteristic for demyelination (i.e. periventricular, juxtacortical, infratentorial or spinal cord). The new criteria were designed in order to simplify and reduce the number of lesions and regions needed for radiological DIS to a minimum (≥1 lesions in ≥2 of the four regions).

The Queen Square group proposal also removed the option to include gadolinium enhancement as a feature of DIS and suggested only T2 lesions and their location be considered. The modified DIT criteria require ≥ one new T2 lesion(s) at three-month follow-up, regardless of when the reference MRI was performed.[4,30] The accuracy of these new criteria was confirmed in the results of a study carried out by the Magnetic Imaging in Multiple Sclerosis (MAGNIMS) group. This study showed similar specificity for CDMS using the Queen Square group criteria compared with the 2005 and 2001 McDonald criteria (87 versus 88 versus 91%, respectively). At the same time, sensitivity was improved (72 versus 60 versus 47%), see *Table 1*.[3]

Although the delay required for a second MRI scan may prevent incorrect and premature diagnosis, there is evidence that the presence of non-enhancing and enhancing lesions on a single MRI, even if obtained within the first three months after the first symptom, could be sufficient to establish DIT. This is because it is likely that this combination reflects lesions in different stages of evolution.[5]

Although highly specific (86%), these criteria have been shown to have a rather low sensitivity (45%). There is also some concern about misdiagnosis, as other entities such as acute disseminated encephalomyelitis can often present with a mixed pattern of enhancing and non-enhancing lesions at the same time point.[31] This new proposal only would therefore only apply to typical CIS occurring between 14 and 50 years of age.

With all the new evidence available, the European multicentre collaborative research network, Magnetic Imaging in MS (MAGNIMS) has proposed new algorithms for MS diagnosis (see *Table 2* and *Figure 1*):[32]

- a MRI scan performed at any time demonstrating DIS and showing at least one asymptomatic gadolinium-enhancing and non-enhancing lesion is evidence for DIT;
- a MRI scan performed at any time and showing DIS, but without any enhancing lesions or with all lesions enhancing, requires a second MRI to demonstrate new T2 or gadolinium-enhancing lesions; and
- a MRI scan performed at any time not showing DIS or DIT requires further follow-up scans to confirm DIS and/or DIT.

The recommended DIS criteria are those proposed by Swanton in 2005.[29] DIT criteria can be fulfilled by:

- the presence of one or more asymptomatic gadolinium-enhancing and non-enhancing lesions, irrespective of the time of the scan; or

- the presence of a new T2 and/or gadolinium-enhancing lesion compared to a previous scan, irrespective of the time of the reference scan.

Implications of the New Criteria

MRI is not only a diagnostic tool but also prognostic tool, as it can predict conversion to CDMS. Therefore, MRI can help in making decisions on the use of disease-modifying drugs. The role of CSF abnormalities, other paraclinical tests and the impact of three Tesla or higher field MRI findings must still be defined in the new guidelines.

Changes in criteria can affect the results of future clinical trials, as was observed in the transition between the Poser and McDonald criteria. An earlier diagnosis of MS based on an MRI may change the disease prognosis when compared with patients diagnosed with MS in the past, but does not really affect the overall prognosis (Will Rogers phenomenon).[33] Such changes in criteria make it difficult to compare the results of studies based on new and old criteria. Despite these concerns, it is hoped that simplifying MS criteria will help neurologists, as the new criteria are easier to implement in daily clinical evaluation and aid in the choice of treatment considered after a first attack. ■

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