

# Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis

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**The International Panel on MS Diagnosis presents revised diagnostic criteria for multiple sclerosis (MS). The focus remains on the objective demonstration of dissemination of lesions in both time and space. Magnetic resonance imaging is integrated with clinical and other paraclinical diagnostic methods. The revised criteria facilitate the diagnosis of MS in patients with a variety of presentations, including “monosymptomatic” disease suggestive of MS, disease with a typical relapsing-remitting course, and disease with insidious progression, without clear attacks and remissions. Previously used terms such as “clinically definite” and “probable MS” are no longer recommended. The outcome of a diagnostic evaluation is either MS, “possible MS” (for those at risk for MS, but for whom diagnostic evaluation is equivocal), or “not MS.”**

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Because no single clinical feature or diagnostic test is sufficient for the diagnosis of multiple sclerosis (MS), diagnostic criteria have included a combination of both clinical and paraclinical studies.<sup>1,2</sup> The last formal review of criteria for MS diagnosis occurred in 1982,<sup>2</sup> at which time degrees of diagnostic certainty were identified by categories ranging from clinically definite diagnosis to laboratory-supported definite MS, clinically probable MS, and laboratory-supported probable MS.

In July, 2000, the International Panel on the Diagnosis of MS was convened in London, United Kingdom, under the auspices of the U.S. National Multiple Sclerosis Society and the International Federation of MS Societies to reassess existing diagnostic criteria and to recommend, if necessary, appropriate changes. The Panel set out to create diagnostic criteria that could be used by the practicing physician and that could be

adapted, as necessary, for clinical trials. The Panel also set out to integrate magnetic resonance imaging (MRI) into the overall diagnostic scheme because of its unique sensitivity to pathological change and to include a scheme for the diagnosis of primary progressive disease<sup>3</sup>—that characterized by the absence of relapses or remissions from onset—because neither had been sufficiently defined or integrated into existing diagnostic criteria for MS. The Panel also sought to clarify certain definitions currently used in the diagnosis of MS and, when possible, to simplify the diagnostic classification and descriptions. While refining the diagnostic criteria to reflect improved understanding of the disease and new technologies, the Panel wished to retain as many as possible of the useful features of existing criteria. Among general outcomes of the discussion, the Panel concluded the following.

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- Obtaining objective evidence of dissemination in time and space of lesions typical of MS is essential in making a secure diagnosis, as is the exclusion of other, better explanations for the clinical features.
- Clinical evidence depends primarily on objectively determined clinical signs. Historical accounts of symptoms may lead to a suspicion of the disease but cannot be sufficient on their own for a diagnosis of MS. A diagnosis of MS on purely clinical evidence remains possible if there is objective evidence of lesions separated in time and space.
- Radiological and laboratory investigations, including MRI, analysis of cerebrospinal fluid (CSF), and visual evoked potentials (VEP), can add to a clinical diagnosis and may be essential in making a diagnosis when clinical presentation alone does not allow a diagnosis to be made. These tests provide different types of information, and their value depends on the context in which the diagnosis is being made. Each has limitations of sensitivity and specificity. Imaging is viewed as the most sensitive and specific of these in making an MS diagnosis. Because CSF adds a different kind of information—about inflammation and immunological disturbance—it may be useful in situations when the clinical picture is unusual or the imaging criteria for diagnosis are not fulfilled. VEP may provide additional support, particularly in situations in which MRI abnormalities are few (eg, in patients with primary progressive MS with progressive myelopathy) or when MRI abnormalities have lesser specificity (eg, in older individuals with risk factors for microvascular ischemic disease or in individuals with abnormal radiological findings that do not satisfy the MRI specificity criteria for diagnosis). Other types of evoked potential analysis were viewed as contributing little to the diagnosis of MS.<sup>4</sup>
- Following a diagnostic evaluation, an individual is usually classified either as having MS or as not having MS. A patient with appropriate clinical presentation who has not yet been evaluated, or whose evaluation meets some but not all of the necessary criteria, is considered to have “possible MS.” Subcategories that define the types of studies used in the diagnostic workup (“clinically definite,” “laboratory supported,” etc.) are unnecessary.

### Definitions

The Panel reviewed definitions used in previous diagnostic criteria to clarify terms for future diagnostic purposes.

### *What Constitutes an “Attack”?*

An “attack” (exacerbation, relapse) refers to an episode of neurological disturbance of the kind seen in MS, when clinicopathological studies have established that the causative lesions are inflammatory and demyelinating in nature. Although there was some divergence of opinion, the group agreed that, for general diagnostic purposes, an attack, defined either by subjective report or by objective observation, should last for at least 24 hours.<sup>2</sup> This assumes that there is expert clinical assessment that the event is not a pseudoattack, such as might be caused by a change in core body temperature<sup>5</sup> or infection. Whereas suspicion of an attack may be provided by subjective historical reports from the patient, objective clinical findings of a lesion are required to make a diagnosis of MS. Single paroxysmal episodes (eg, a tonic spasm) do not constitute a relapse, but multiple episodes occurring over not less than 24 hours do.

### *How Is the Time Between Attacks Measured?*

In defining what constitutes separate attacks, for the purposes of documenting separation in time of such events, it was agreed that 30 days should separate the onset of the first event from the onset of a second event. This interpretation has the advantage of being less ambiguous than considering the interval from beginning of recovery from the first event to initiation of the second event, as suggested in the definition of the “Poser Committee.”<sup>2</sup>

### *How Is “Abnormality” in Paraclinical Tests Determined?*

MRI. Lesions in the brain detected by MRI can provide evidence of dissemination of lesions in both time and space. It was agreed that stringent criteria for MRI abnormality should be followed in making an MS diagnosis. From among those that have been proposed, the Panel preferred those derived from the studies of Barkhof et al<sup>6</sup> and Tintoré et al,<sup>7</sup> which require evidence of at least three of four of the following: 1) one gadolinium-enhancing lesion or nine T2 hyperintense lesions if gadolinium-enhancing lesions are not present; 2) at least one infratentorial lesion; 3) at least one juxtacortical lesion (ie, involving the subcortical u-fibers); 4) at least three periventricular lesions (see Table 1). Lesions will ordinarily be larger than 3 mm in cross section. These criteria provide an acceptable degree of sensitivity while providing greater specificity and accuracy<sup>7</sup> than the MRI criteria proposed by Fazekas et al<sup>8,9</sup> and Paty et al.<sup>10</sup>

The assessment of dissemination in time is discussed below in relation to each particular mode of clinical presentation (see Table 2). The criteria derived from Barkhof et al<sup>6</sup> do not deal with lesions detected in the

Table 1. Magnetic Resonance Imaging Criteria for Brain Abnormality

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Three of four of the following

1. 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

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Note: One spinal cord lesion can be substituted for one brain lesion. Data from Barkhof et al<sup>6</sup> and Tintoré et al.<sup>7</sup>

spinal cord. Prospective data are currently insufficient to define more precisely the role of spinal cord lesions in diagnosis. However, the characteristics and distribution of spinal cord lesions in MS are well-described, as is their absence in healthy controls, even among older adults.<sup>11</sup> There should be little or no swelling of the cord, although exceptions occur, and such spinal lesions should be unequivocally hyperintense on T2-weighted images, be at least 3 mm but under two vertebral segments in length, and occupy only part of the cross section of the cord.<sup>12</sup> Accordingly, spinal cord lesions detected by MRI might, in some situations (such as in clinically isolated syndromes<sup>13</sup> or when disease is progressive from onset<sup>3</sup>), supplement incomplete information from brain MRI scans. Whereas it is possible that, in the absence of brain lesions, two or more spinal cord lesions clearly separated in time and/or space could satisfy criteria, prospective data in this regard are still awaited. It is expected that with further research the necessary information on sensitivity and specificity of spinal cord images for MS diagnosis will be available.

**CSF ANALYSIS.** Abnormality on CSF analysis can provide supportive evidence of the immune and inflammatory nature of lesion(s), which may be helpful when imaging criteria fall short, when they lack specificity (as in the older patient), or when the clinical presentation is atypical. CSF analysis cannot provide information about dissemination of lesions or events in time or space.

For the purpose of diagnosing MS, CSF abnormality is defined (preferably using isoelectric focusing) by the presence of oligoclonal IgG bands different from any such bands in serum and/or the presence of an elevated IgG index.<sup>14,15</sup> Lymphocytic pleocytosis should be less than 50/mm<sup>3</sup>. It is recognized that the quality of CSF analysis is not uniform among laboratories, regions, or countries. It is the practitioner's obligation, when including results of such analyses, to ensure that they are being done in the most reproducible fashion, with state-of-the-art technology. Failure to do so might result in unreliable measurement and incorrect diagnosis.

**VEP.** Abnormal VEP, typical of MS (delayed but with well-preserved wave form<sup>16</sup>), can be used to supple-

ment information provided by a clinical examination<sup>4</sup> to provide objective evidence of a second lesion provided that the only clinically expressed lesion did not affect the visual pathways. As with MRI and CSF analysis, correct interpretation is essential.

### The Diagnostic Scheme

Table 3 indicates the steps that should be undertaken in making a diagnosis of MS. In this scheme, the mode of clinical presentation is indicated in the left column. The data needed to make an MS diagnosis are indicated, for each presentation, in the right column. Failure to satisfy the criteria for an MS diagnosis will result in either a "possible MS" diagnosis, pending further analysis, or classification as "not MS." The order in the table of "clinical presentation" is deliberate; the Panel believes that a diagnosis is simplest in the case of "two attacks, clinical evidence of two or more lesions" and becomes increasingly difficult through "insidious neurological progression suggestive of MS." The additional criteria needed to make a diagnosis of MS, therefore, become more stringent as the clinical evidence upon presentation becomes weaker. As is made clear below, follow-up with additional clinical assessments, laboratory investigation, and in particular MRI is important when a diagnosis cannot be made on clinical criteria alone at first presentation.

#### *Two or More Attacks, Objective Clinical Evidence of Two or More Lesions*

Two clear attacks typical of MS, documented by objective evidence of two lesions separated in time and necessarily separated in space may be sufficient to make an MS diagnosis solely on clinical grounds. No additional tests may be needed. However, it would be expected that

Table 2. Magnetic Resonance Imaging Criteria for Dissemination of Lesions in Time

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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.<sup>22</sup> 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 more 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.
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Table 3. Diagnostic Criteria

Clinical Presentation	Additional Data Needed for MS Diagnosis
Two or more attacks; objective clinical evidence of 2 or more lesions	None <sup>a</sup>
Two or more attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by MRI <sup>b</sup> <i>or</i> Two or more MRI-detected lesions consistent with MS plus positive CSF <sup>c</sup> <i>or</i> Await further clinical attack implicating a different site
One attack; objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by MRI <sup>d</sup> <i>or</i> Second clinical attack
One attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by MRI <sup>b</sup> <i>or</i> Two or more MRI-detected lesions consistent with MS plus positive CSF <sup>c</sup> <i>and</i> Dissemination in time, demonstrated by MRI <sup>d</sup> <i>or</i> Second clinical attack
Insidious neurological progression suggestive of MS	Positive CSF <sup>c</sup> <i>and</i> Dissemination in space, demonstrated by 1) Nine or more T2 lesions in brain <i>or</i> 2) 2 or more lesions in spinal cord, <i>or</i> 3) 4–8 brain plus 1 spinal cord lesion <i>or</i> abnormal VEP <sup>e</sup> associated with 4–8 brain lesions, or with fewer than 4 brain lesions plus 1 spinal cord lesion demonstrated by MRI <i>and</i> Dissemination in time, demonstrated by MRI <sup>d</sup> <i>or</i> Continued progression for 1 year

If criteria indicated are fulfilled, the diagnosis is multiple sclerosis (MS); if the criteria are not completely met, the diagnosis is “possible MS”; if the criteria are fully explored and not met, the diagnosis is “not MS.”

<sup>a</sup>No additional tests are required; however, if tests [magnetic resonance imaging (MRI), cerebral spinal fluid (CSF)] are undertaken and are *negative*, extreme caution should be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture.

<sup>b</sup>MRI demonstration of space dissemination must fulfill the criteria derived from Barkhof et al<sup>6</sup> and Tintoré et al<sup>7</sup> (see Table 1).

<sup>c</sup>Positive CSF determined by oligoclonal bands detected by established methods (preferably isoelectric focusing) different from any such bands in serum or by a raised IgG index.<sup>14,15</sup>

<sup>d</sup>MRI demonstration of time dissemination must fulfill the criteria listed in Table 2.

<sup>e</sup>Abnormal visual evoked potential of the type seen in MS (delay with a well-preserved wave form).<sup>16</sup>

one or more such tests—MRI, CSF, or VEP—would be abnormal were they done. If these tests are undertaken and are *not* abnormal in a manner typical of MS, extreme caution must be taken in making a diagnosis of MS. It must be stressed that there should be no better explanation than MS for the clinical picture.

#### *Two or More Attacks, Objective Clinical Evidence of One Lesion*

To make a diagnosis of MS, objective evidence of a second lesion is required to demonstrate dissemination

in space. This can be provided by an MRI scan of the brain fulfilling criteria derived from Barkhof et al<sup>6</sup> and Tintoré et al<sup>7</sup> (see Table 1). A spinal cord lesion can be substituted for one of the brain lesions. Alternatively, should MRI data fall short of these requirements, the presence of at least two brain lesions or one brain and one spinal cord lesion consistent with MS, coupled with abnormal CSF analysis (to avoid misdiagnosing nonspecific vascular lesions as inflammatory), can be used to document dissemination in space. Alternatively, if MRI is not performed, the occurrence of a

further clinical attack implicating a different site will fulfill criteria for dissemination in space.

#### *One Attack, Objective Clinical Evidence of Two or More Lesions*

To make a diagnosis of MS, dissemination in time must be demonstrated. This can be done by MRI, although careful consideration must be given to the timing of the clinical event and subsequent scans (see Table 2). There must be a minimum of 3 months between the clinical event and evidence for a new lesion. (This interval is arbitrary, but it reduces the risk of misdiagnosing MS in cases of acute disseminated encephalomyelitis with a stuttering onset.<sup>17</sup>) Alternatively, if MRI tests are not performed, the occurrence of a second clinical attack is necessary to fulfill criteria for dissemination in time.

#### *One Attack, Objective Clinical Evidence of One Lesion*

To make a diagnosis of MS, dissemination of lesions both in space and in time will have to be demonstrated. The typical situation is the patient presenting solely with a clinically isolated syndrome suggestive of MS (so-called monosymptomatic presentation). A diagnosis of MS then requires 1) evidence of dissemination in space through detection of lesions using MRI as described above (see also Table 1) or, lacking such solid evidence, at least two brain lesions plus positive CSF, and 2) evidence of dissemination in time demonstrated as for the patient presenting with one attack and clinical evidence of two lesions (see above and Tables 2, 3). In this situation as well, if MRI tests are not performed, the occurrence of a second clinical attack implicating a different site will fulfill criteria for dissemination in time and space.

#### *Insidious Neurological Progression Suggestive of Multiple Sclerosis*

This is often a difficult presentation for a diagnosis of MS, in that typical relapses are absent and dissemination in time and in space of separate events may be difficult to determine. The Panel had particular difficulty in reaching a consensus on the criteria for diagnosis in this clinical group, because the amount of published follow-up data for this is much less than for other modes of clinical presentation. For this reason, the stringent criteria proposed in a recent position paper<sup>3</sup> serve as the basis for the proposed diagnostic criteria. The Panel recognizes that modifications may be appropriate as more information becomes available.

With this mode of clinical presentation, to make a secure diagnosis of MS, the majority of the Panel considered that an abnormal CSF finding with evidence of inflammation and immune abnormality is essential and that evidence is required of dissemination in space (us-

ing MRI or abnormal VEP) and time (using MRI or continued progression of disability for 1 year). When these criteria are fulfilled, the diagnosis is “primary progressive MS” (see Table 3).

#### *No Better Explanation*

The Panel emphasizes that, even if the clinical evidence and paraclinical studies are strongly indicative of MS, there must be *no better explanation* for the clinical and paraclinical abnormalities than MS for a secure diagnosis to be made.

#### **Discussion**

The diagnosis of MS has traditionally relied upon accumulation of information, clinical and paraclinical, that leads to a positive diagnosis and can help to eliminate alternative diagnoses. Among the key indicators is evidence that the disease is inflammatory, whether recurrent or progressive. The International Panel on the Diagnosis of MS reaffirms the need to demonstrate dissemination of clinical events and lesions in space and time, long-held criteria for MS diagnosis, and the diagnostic scheme presented is organized to emphasize this point. Requiring objective clinical evidence of attacks or progression (symptoms alone are not enough) is a renewed emphasis but one that the Panel believes is essential because of the implications of the diagnosis of MS for treatment.

The criteria presented in this report are intended for use by the practicing physician, and it is expected that in most cases these clinicians will have access to the technologies required for the diagnostic workup. However, the Panel recognizes that in some parts of the world access to advanced technologies such as MRI is limited; if so, and if no alternatives to imaging (such as analysis of CSF and VEP) are available, a diagnosis of “possible MS” will be made until the subsequent clinical course allows the criteria of at least two attacks and clinical evidence of at least two separate lesions to be fulfilled.

It is further recognized that the methods and sensitivity of paraclinical testing and analysis vary worldwide. The Panel’s recommendations are predicated on the availability of highest quality, state-of-the-art technology related to imaging, CSF analysis, and evoked potential recording. For example, in the use of imaging to document dissemination of lesions in time, accurate repositioning and coregistration of scans may be necessary to determine whether some of the lesions appearing on a follow-up scan are new.<sup>18</sup> When a physician is not ensured of the quality and reproducibility of any paraclinical analyses, extreme care must be taken in using the results as evidence supporting a diagnosis of MS. It is hoped that these recommendations will encourage greater uniformity and reliability in the use of such technologies.

The Panel's recommendations represent a pragmatic approach to allow a diagnosis of MS in the most typical clinical presentations. It is important to note that the recommendations are based on data and experience available primarily from adults with typical features of MS and that these criteria would best apply to individuals between 10 and 59 years of age and in cases in which the clinical presentation is reasonably suggestive of MS. Special care must be taken in making a diagnosis of MS in those who are younger or older at presentation, those with a progressive onset, and those with unusual features or an "atypical" presentation, such as dementia, epilepsy, or aphasia. In such cases, additional evidence from CSF and VEP analysis may help in attaining security about a diagnosis of MS, even if these are not required for the more typical cases. For unusual cases, the importance of follow-up assessments cannot be overemphasized.

Several MS-like presentations and clinical syndromes present particular difficulties in considering a diagnosis of MS. A detailed discussion of differential diagnosis is beyond the scope of this paper, and the reader is referred to standard accounts of differential diagnosis.<sup>19</sup> Nevertheless, several conditions that may be confused with MS should be kept in mind in assessing a patient for an MS diagnosis. These include multifocal areas of cerebral ischemia or infarction in young adults from such illnesses as phospholipid antibody syndrome, acute disseminated lupus erythematosus, CADASIL, Takayasu's disease, meningovascular syphilis, or even carotid dissection. Various infections such as HTLV1 and Lyme disease can present striking similarities to MS. Cerebellar ataxia presenting as a result of a paraneoplastic disorder in young adults may be a problem, especially because elevated IgG often occurs in the CSF in this illness. Monophasic demyelinating diseases such as acute disseminated encephalomyelitis, postviral Devic's syndrome, and some cases of acute transverse myelitis present special difficulties in diagnosis; a diagnosis should not be made in these circumstances unless new symptoms and signs or imaging abnormalities appear more than three months after clinical onset. Some regard recurrent demyelinating diseases such as acute disseminated encephalomyelitis with a stuttering onset, neuromyelitis optica (Devic's syndrome<sup>20</sup>), and recurrent longitudinally extensive transverse myelitis as separate diseases, but others regard them as variants of MS. Genetic disorders of myelin, such as the leukodystrophies, should be considered in certain settings, particularly among children and teenagers.

Clinical trials for evaluating new therapeutic agents and other clinical experimental protocols may require different diagnosis-related inclusion and exclusion criteria than those provided in the present recommended basic steps. Given the wide variation in presentation of MS, there must be some flexibility in the application of

the new diagnostic scheme. A secure diagnosis, however, should be based on the elements presented here. It must always be remembered that there should be no better explanation for the clinical and investigative data obtained.

Whereas it might be said that the only proved diagnosis of MS can be made upon autopsy,<sup>21</sup> or occasionally upon biopsy, where lesions typical of MS can be directly detected through standard histopathological techniques, MS is essentially a clinical problem and can be diagnosed using clinical and paraclinical criteria. Biopsy is a diagnostic technique that can confirm that a lesion is inflammatory and demyelinating (though it cannot on its own lead to a diagnosis of MS) and should *rarely* be undertaken. Interpretation by neuropathologists experienced in the demyelinating diseases is essential in avoiding misdiagnosis.

Imaging undertaken for other purposes occasionally uncovers "silent disease." When such silent cases are uncovered, some degree of monitoring may be desirable.

The International Panel on MS Diagnostic Criteria built upon diagnostic recommendations for MS that have served the community well for decades. Key points include a continued emphasis on dissemination of lesions in time and space and on the value of paraclinical testing, especially imaging, as a key part of the overall diagnostic workup. Specific imaging criteria are presented. However, the diagnosis of MS remains a partly subjective and partly objective process. The diagnosis is best made by an expert who is familiar with the disease, its differential diagnoses, and the interpretation of paraclinical assessments (imaging, CSF analysis, and evoked potentials) that can supplement the diagnostic process.

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