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Review

Revised diagnostic criteria of multiple sclerosis

Ron Milo [a,*], Ariel Miller [b,c]

[a] Department of Neurology, Barzilai Medical Center, Ashkelon, Faculty of Health Sciences, Ben-Gurion University of the Negev, Israel
[b] Multiple Sclerosis & Brain Research Center, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Carmel Medical Center, Haifa 34362, Israel
[c] Department of Neurology, Carmel Medical Center, Haifa 34362, Israel

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ABSTRACT

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) of presumed autoimmune etiology, characterized by localized areas of inflammation, demyelination, axonal loss and gliosis in the brain and spinal cord. Although the clinical presentation and course of the disease are highly variable, several disease types can be recognized, including relapsing–remitting—(RR), primary–progressive—(PP), secondary–progressive—(SP), progressive–relapsing—(PR) MS and clinically-isolated syndrome (CIS). There is no single clinical feature or diagnostic test that is sufficient to diagnose MS, and the diagnosis is mainly a clinical one. Over the years, several sets of criteria have been proposed for the diagnosis of MS, based on the principles of dissemination in space (DIS) and dissemination in time (DIT) of CNS lesions, and the exclusion of other diseases with similar characteristics. With each revision, new diagnostic criteria modified disease definitions and diagnostic thresholds, while aiming at maintaining sensitivity and improving specificity. According to the older Schumacher and Poser criteria, MS can be diagnosed clinically by demonstrating 2 separate attacks (fulfilling DIT criteria) involving at least 2 different areas of the CNS (fulfilling DIS criteria). The 2001 McDonald criteria and their 2005 revision incorporated defined magnetic resonance imaging (MRI) criteria for DIS and DIT that provided guidance on how to diagnose MS after CIS. The most recent 2010 McDonald criteria simplify requirements for DIS and DIT and may allow for an earlier diagnosis of MS from a single baseline brain MRI if there are both silent gadolinium-enhancing and nonenhancing lesions. Despite these important advances in the diagnosis of MS, some questions still remain regarding the application and the implications of the new criteria in the daily clinical practice and in clinical trials. Most importantly, thorough clinical evaluation and judgment along with careful differential diagnosis still remain the basics in the diagnosis of MS.

Contents

1. Introduction

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease of the central nervous system (CNS) characterized pathologically by perivascular infiltrates of mononuclear cells, demyelination, axonal

* Corresponding author at: Department of Neurology, Barzilai Medical Center, 2 Hahistadrut St. Ashkelon 78278, Israel. Tel.: +972 8 674 5117; fax: +972 8 674 5463.
E-mail address: rmilo@barzi.health.gov.il (R. Milo).

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loss and gliosis with the formation of multiple plaques in the brain and spinal cord, and clinically by a variety of neurological signs and symptoms disseminated in time and space. Recent advances in understanding the etiology and pathogenesis of MS contributed to better diagnosis and a plethora of therapies that substantially affect disease activity and may have a long-term impact on the course and prognosis of MS. The routine use of magnetic resonance imaging (MRI) as a diagnostic tool and a surrogate measure, the recognition of the need for early diagnosis and treatment of MS and the identification of clinical and imaging prognostic factors resulted in several revisions of the diagnostic criteria for MS, aiming at as early and accurate as possible diagnosis of this weighty disease.

2. History

The history of MS resembles a journey created by a series of careful observations, discoveries and scientific achievements [1]. The first recorded description of MS dates back to 1421 with the case of Saint Lidwina of Schiedan (1380–1433) who developed symptoms and disease course consistent with MS when she was 16 after falling and breaking a rib when ice-skating. In his diary, Sir Augustus d'Este (1794–1848) documented his own 26-year undiagnosed illness that appeared after a bout of measles and included visual impairment, numbness below the waist, ataxia, fatigue, spasms at night and progressive loss of motor control. "A peculiar disease state of the chord and pons Varolii, accompanied with atrophy of the discolored portions" was described in 1838 by the Scottish pathologist Robert Carswell who also described and illustrated many of the clinical details of MS but did not identify it as a separate disease. The French anatomist Jean Cruveilhier (1791–1874) depicted the pathological features of "disseminated sclerosis" in another case of a woman who developed weakness in 4 limbs, spasms, visual disturbances and dysphagia, before the first diagnosis of MS in a living human being was made by the German pathologist Friedrich von Frerichs in 1849 and validated by his student Valentiner in 1856. The "Father of Neurology", Jean Martin Charcot of La Salpétrière hospital in Paris was the first to make the story of MS coherent. In a series of original articles published in 1868 on "La sclerose en plaques" [2], and later in his published lectures and clinical presentations [3], he made definite links between the diverse symptomatology of the disease and its pathological changes, recognizing inflammatory cells, loss of myelin, proliferation of glial fibers and nuclei, and axonal damage, alongside clinical features, including cognitive decline. Charcot recognized that multiple sclerosis was a distinct entity; he gave it nosological status, made accurate clinicopathological correlations, emphasized its frequency, speculated on the pathophysiology, and despaired of effective treatment. His observations led also to the development of the first diagnostic criteria for MS, namely the Charcot triad (nystagmus, ataxia and dysarthria). Charcot's greatest pupil and successor as Chair of Neurology at the Salpêtrière hospital, Pierre Marie, suggested in 1884 the infectious etiology for MS, which is still considered most likely. Russel Brain, in the 1933 first edition of his textbook "Diseases of the Nervous System", provided data on the incidence and course of MS with accurate accounts of the underlying pathology and comprehension of the disease which stand almost unchanged until today.

The hypothesis that MS involves an autoimmune response to a self-antigen in genetically susceptible individuals induced by a hitherto unknown environmental-infectious agent evolved during the 20th century as a result of several discoveries, including the ability to induce an MS-like autoimmune disease in mammals by immunization with myelin or myelin antigens from the CNS (experimental autoimmune encephalomyelitis, EAE) in 1933 [4], the description of inflammatory changes in the cerebrospinal fluid (CSF), the detection of increased proportion of gamma globulins in the CSF of MS patients using electrophoresis in 1948 [5], and several later large epidemiological and twins studies. The successful introduction of ACTH corticosteroids for the treatment of MS relapses in the 60's, and the introduction of long-term treatment with immunosuppressive drugs in the 70's of the 20th century added support to the theory of the immune-mediated nature of MS. The application of MRI during the last 33 years dramatically improved our ability to visualize MS lesions in the brain and spinal cord, and the continuous introduction of non-conventional MRI techniques, may now allow for more accurate measurements of axonal loss, atrophy or the so-called "normal-appearing" brain tissue.

Interferon beta-1b, the first effective preventive treatment for MS, has been introduced in 1993, signaling the way to many current and future promising disease modifying agents. The currently used McDonald criteria for MS were first published in 2001 and then reviewed twice — in 2005 and 2010.

3. The disease

MS is a heterogenous disease characterized by a wide variety of neurological symptoms and signs attributed to discrete areas of inflammation, demyelination, axonal loss and gliosis ("plaques") distributed in the CNS. A key feature of MS which is central to the diagnosis of the disease is that lesions are disseminated both in time and in space.

3.1. Epidemiology

MS affects mainly young people with onset usually at the age of 20–50 and a mean age of onset of 30, although the disease may develop also in childhood and after the age of 60, and is 3 times more common in females than in males. The cause of MS is still unknown. However, genetic, environmental and immunological factors have been implicated in the etiology of the disease [reviewed in 6]. The total number of people living with MS worldwide is estimated to be 2.5 million, which are unevenly distributed throughout the world. The prevalence of MS follows a latitudinal gradient in an incomplete distribution model, and varies from less than 5/100,000 in low-risk areas (e.g. most of Africa and Eastern Asia), to more than 100/100,000 in high-risk areas (e.g. northern and central Europe, North America and Southeastern Australia). Migration studies indicate that immigrants tend to develop a prevalence rate similar to that of the indigenous population, especially if they have migrated before puberty [7]. Additionally, several clusters and "epidemics" of MS have been reported [8]. Taken together, these observations support environmental factors in the etiology of MS, the most plausible ones include exposure to the Epstein–Barr virus (EBV) after early childhood and manifestations of infectious mononucleosis, reduced exposure to sunlight and ultraviolet radiation, vitamin D deficiency and cigarette smoking [6]. Recent studies suggest also a role for dietary sodium in inducing pathogenic Th17 cells [9,10] which may partially account for the observed worldwide increase in MS incidence. A wide variety of other environmental factor have also been suggested as triggers for MS, but their role is disputed [6].

3.2. Genetics

MS is a complex genetic disease. Several genetic studies show familial aggregation in MS, increased risk of having MS among relative of MS patients and a concordance rate of 30% among monozygotic twins. The high prevalence of MS in areas settled by the Vikings around the world, the rarity of MS in certain races and pockets of low prevalence in high risk areas (e.g. African–Americans or Indians in America, gypsies in central Europe or Lapps in Norway) also support genetic susceptibility to MS. The strongest association maps to the HLA–DRB1 allele of the class-II major histocompatibility complex region, which suggests an autoimmune etiology for MS. Genome wide association studies have identified more than 100 additional variants, predominantly associated with the immune system, all of which have modest individual effects. Multiple explanations for the missing heritability in MS have been proposed, including gene by gene and gene by environment interactions, cis/trans regulators of allelic expression, unidentified rare and penetrant semi-private variants,

population and/or disease heterogeneity, genes of interest in 'problematic' genomic regions, neglecting the analysis of sex chromosomes, and epigenetic effects. [11].

3.3. Clinical features and prognosis

MS patients show a wide variety of neurological symptoms and signs that originate in different parts of the CNS and may occur alone or in combination, as sudden attacks or as part of a steady progression. Common presenting symptoms include paresthesias or numbness, motor weakness, monocular visual disturbances, diplopia, incoordination, gait disturbances, dizziness and vertigo. Other accompanying symptoms and signs may include fatigue, spasticity, ataxia, nystagmus, sensory loss, neuropathic pain, urinary urgency or retention, sexual dysfunction, depression or other emotional changes, heat intolerance, Lhermitte's phenomenon, cognitive dysfunction, and more [12,13]. Continuous pathological activity is almost invariably associated with disease progression and accumulation of disability over time, with a median time of 10 years to reach walking impairment and 15–20 years to reach unilateral support for walking [expanded disability status scale (EDSS) score of 6.0]. Eventually, most patients will require some mobility assistance [14]. Life expectancy is reduced by an average of 7–10 years, and the main causes of death are medical complications of the disease in 50% of the patients, suicide and causes similar to those in the general population.

A number of prognostic factors have been reported to predict a worse prognosis or more rapid disease progression in MS or in the conversion from CIS to definite MS [13,15], including: Age >40 at disease onset; male gender; ethnic origin (Asians or African–Americans); initial presentation with motor, cerebellar or sphincter symptoms or polyregional symptoms; incomplete recovery from initial attacks; frequent attacks during the first years of the disease; short interval between the first two attacks; rapid disability progression during the first years; progressive disease from onset; cognitive impairment at disease onset; the presence of oligoclonal immunoglobulins in the CSF and high burden of disease or gadolinium (Gd) enhancement on initial MRI.

3.4. Disease course

Although the clinical course of the disease is highly variable, four disease types can be recognized [16]:

- Relapsing–remitting MS (RRMS): clearly defined attacks of new or recurrent neurologic symptoms and signs with full or partial recovery and lack of disease progression between disease relapses. This type accounts for approximately 80–85% of initial diagnoses of MS.
- Primary–progressive MS (PPMS); disease progression from onset with occasional plateaus and temporary minor improvements allowed. Approximately 10–15% of MS patients have PPMS.
- Secondary–progressive MS (SPMS): initial RR disease course followed by progression with or without occasional relapses, minor remissions, and plateaus. Approximately 50% of RRMS patients convert to SPMS after 10 years and 90%—after 25 years [17].
- Progressive–relapsing MS (PRMS): progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses characterized by continuing progression. PRMS may present a subtype of PPMS as they share a similar natural history [13,18].

Additional MS subtypes include:

- Clinically isolated syndrome (CIS): a first clinical episode suggestive of MS [19].
- Radiologically isolated syndrome (RIS): the incidental finding of typical MS lesions on MRI without evidence of clinical disease. Sometimes refers to as asymptomatic or pre-clinical MS [20].
- Benign MS: this highly debated concept is defined as a disease in which the patient remains fully functional in all neurologic systems 15 years after disease onset [16].
- Malignant (fulminant) MS: disease with a rapid progressive course, leading to significant disability in multiple neurologic systems or death in a relatively short time after disease onset [16].
- Single-attack progressive MS: a rare condition generally considered to be a subtype of SPMS in which a single initial attack is followed by the progressive phase [13].
- Transitional MS: the transition phase between RRMS and SPMS, reflecting the fact that this is often a gradual process [13].

3.5. Pathology and pathogenesis

MS plaques can occur anywhere in the CNS, in the white matter around the ventricles, optic nerves and tracts, corpus callosum, cerebellar peduncles, long tracts and subpial regions of the spinal cord and brainstem, but also in the gray matter. These plaques are composed of perivenular infiltrates of mononuclear inflammatory cells (T-lymphocytes, monocytes/macrophages, B and plasma cells), demyelinated axons, reduced number of oligodendrocytes, transected axons, and astrocyte proliferation with resultant gliosis. MS lesions may be divided into acute, chronic active and chronic silent. They show profound heterogeneity in the structural and immunopathological patterns of demyelination and oligodendrocyte pathology between different MS patients [21], suggesting that MS is a neurologic syndrome rather than a single disease.

Traditionally, MS has been considered a T-cell mediated autoimmune disease. It has become apparent recently that its pathogenesis is far more complex, involving all arms of the innate and adoptive immune system with slowly progressive neurodegeneration in addition to acute inflammation [22,23].

MS probably begins with the activation of autoreactive CD4+ T helper type 1 (Th1) cells directed against CNS antigens in the periphery. The activated immune cells upregulate surface cell adhesion molecules and cytokine receptors and secrete pro-inflammatory cytokines such as interleukin-2 (IL-2), interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) as well as chemokines and matrix metalloproteinases (MMPs) which provoke reciprocal changes in endothelial cells, enable adherence of the activated cells to the endothelium and facilitate their migration across the blood–brain barrier. The critical role of another T cell lineage for inflammation and disease in the CNS, Th17 cells, has also been recently established. After entering the CNS, the autoreactive T-cells may be reactivated by resident antigen presenting cells (APC) such as microglia or by invading dendritic cells presenting the local CNS antigen(s). This reactivation results in the recruitment and activation of additional cells to the areas of inflammation (e.g. B-cells, myeloid sells, natural killer [NK] cells), the secretion of various cytokines, chemokines, matrix metalloproteinases (MMPs) and other mediators, and the activation of resident microglia and astrocytes. In addition, a large number of MHC class-II restricted CD8+ cytotoxic T-cells recognizing myelin proteins are present both at the inflammatory lesions edge and perivascular regions, that amplify the damage for myelin, oligodendrocytes and axons by antigen specific and non-antigen specific (bystander) injury. Although B-cells comprise only small portion of the inflammatory infiltrate, they also play an important role in the inflammatory response by being a source of plasma cells and anti-myelin antibodies which contribute to myelin injury through complement fixation or antibody-dependent cytotoxicity, serving as potent APC, secreting important cytokines and regulating T-cells and antigen presentation. Damage may also be mediated in a non-antigen specific manner by infiltrating macrophages, mast cells or reactive microglia and their toxic products, and by a variety of other humoral factors. Indirect damage to supporting astrocytes may also occur by NK-cells.

Defective regulation of the immune response is also implicated in the pathogenesis of MS. Several subsets of regulatory T-cells (Treg cells) have been shown to be dysfunctional in patients with MS, resulting in impaired ability to combat destructive inflammation.

T cells with the Th2 phenotype are also recruited to sites of inflammation and down-regulate activated Th1 effector cells by producing anti-inflammatory cytokines. They also secrete relatively high levels of neurotrophic factors which are believed to contribute to repair mechanisms and neuroprotection. There is also evidence for the presence of phenotypically polarized macrophages (M1 and M2) that can drive Th1 or Th2 cell responses as well as differential responses of B-cells.

3.6. Diagnosis

The diagnosis of MS is primarily clinical and relies on the demonstration of symptoms and signs attributable to white matter lesions that are dissemination in time and space, along with the exclusion of other condition that may mimic MS. There is no single laboratory test diagnostic for MS; however, several tests may support the clinical diagnosis: CSF analysis shows increase in immunoglobulin concentrations and 2 or more oligoclonal bands (OCBs) in more than 90% of the patients. Delayed latencies of the visual, somatosensory and auditory evoked potentials on electrophysiological studies, as well as prolonged central motor conduction times, are characteristic of demyelination, and may point to clinically silent lesions. Blood tests are usually used to rule out other diseases which can mimic MS.

3.7. Imaging

MRI is the most sensitive test to detect and demonstrate MS lesions. It is used to support the diagnosis, estimate lesion load and disease activity, measure brain atrophy and axonal loss, follow disease progression, provide prognosis, serve as a surrogate marker and provide outcome measures in clinical trials. MS lesions are hyperintense on T2-weighted, proton density or FLAIR imaging, and hypointense or isointense on T1-weighted imaging. They are typically ovoid in shape, of small size (3–8 mm on average, although giant plaques may occur), located mainly in the periventricular white matter but are also common in the posterior fossa, spinal cord and in subcortical location. They tend to be perpendicular to the ventricles, involve the corpus callosum and U-fibers, and may enhance with Gd, especially during active inflammation, due to disruption of the BBB. Newer MRI techniques facilitated the detection of both gray matter and white matter microstructural damage, and combined histopathologic-MRI correlation studies helped to clarify pathological specificity and sensitivity of these techniques [24].

4. Diagnostic criteria

Diagnostic criteria comprise a need and a challenge in a heterogenous disease such as MS where no single clinical feature or diagnostic test is sufficient to make the diagnosis. Since the days of Charcot, several sets of criteria have been proposed to diagnose MS and distinguish it from other conditions. Schumacher et al. [25] made the first attempt to standardize criteria in 1965 by introducing the fundamental concepts of dissemination in time (DIT) and dissemination in space (DIS), by defining a relapse (lasting at least 24 h and separated by at least 30 days from another relapse), and by including the caveat of "The signs and symptoms cannot be explained better by another disease process" (Table 1). The Poser criteria which followed in 1983 [26] incorporated paraclinical tests (evoked potentials) and spinal fluid evaluations into the clinical criteria to document asymptomatic damage in the central nervous system, thereby confirming dissemination in time and space (Table 2).

The availabiliy of new and effective therapies, the need for early diagnosis and treatment and the use of MRI as a central tool in MS prompted revision to the widely used Poser criteria. An International Panel on the Diagnosis of Multiple Sclerosis, chaired by Dr. W. Ian McDonald, convened in July of 2000 under the auspices of the U.S. National MS Society and the International Federation of MS Societies

Table 1
Schumacher criteria 1965 [25].

6 criteria required for a diagnosis of clinically-definite MS:
1. Objective abnormalities on neurological examination attributable to dysfunction of the CNS; symptoms alone are not sufficient for a diagnosis.
2. At neurological exam or in medical history, there must be evidence of involvement in 2 or more separate parts of the CNS
3. Objective evidence of CNS disease must be predominantly of the white matter, with more than minor gray matter involvement disqualifying.
4. Involvement of the neuraxis must have occurred temporally in one of the following patterns: • 2 or more episode of worsening (relapse), separate by a period of one month or more, each episode lasting at least 24 h. • Slow or step-wise progression of signs and symptoms over at least 6-months.
5. The age of the patient must be within 10–50 years.
6. The signs and symptoms cannot be explained better by another disease process.

to reassess the Poser criteria and recommend, if necessary, appropriate changes [27]. 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; to integrate MRI into the overall diagnostic scheme; to include a scheme for the diagnosis of PPMS; to clarify certain definitions currently used in the diagnosis of MS; and, when possible, to simplify the diagnostic classification and descriptions of MS. While the new criteria still relied on the objective demonstration of dissemination of lesion in both time and space, MRI has been integrated with clinical and other paraclinical diagnostic methods to facilitate the diagnosis of MS in patients with a variety of presentations, including "monosymptomatic" disease suggestive of MS (CIS) and PPMS (Table 3). Previously used terms such as "clinically definite" and "probable MS" were no longer recommended, and the outcome of a diagnostic evaluation was changed to either "MS", "possible MS" (for those at risk for MS, but for whom diagnostic evaluation is equivocal), or "not MS". For the definition of DIS, the panel chose to use the Barkhof–Tintoré MRI criteria for brain abnormalities in MS (three of the four: ≥ 1 Gd-enhancing or ≥ 9 T2-hyperintense lesions, ≥ 1 infratentorial, ≥ 1 juxtacortical, and ≥ 3 periventricular lesions [28,29]), or the presence of 2 silent T2-weighted brain lesions and OCBs in the CSF. In cases of one attack and/or clinical evidence of only one lesion or in patients with insidious neurological progression suggestive of PPMS, DIT could be determined by a Gd-enhancing or a new T2 lesion detected on repeat MRI done 3 or more months after the baseline.

The 2001 Mcdonald criteria enabled an earlier diagnosis of MS in many cases of CIS and showed high specificity (83%), sensitivity (83%), positive predictive value (PPV, 75%), negative predictive value (NPV, 89%) and accuracy (83%) values for the development of MS after CIS [30]. Nevertheless, they were widely criticized for rejecting historical accounts of symptoms, recommending the isoelectric focusing technique with its high false positive rate for CSF analysis of oligoclonal IgG bands, the need for positive CSF for the diagnosis of PPMS which may result in underdiagnosis of this type of MS, and the arbitrary and not evidence-based criterion of 30-day interval to separate between attacks. Moreover, the Barkhof–Tintoré criteria were based on studies that included a small number of "typical" European patients who converted from CIS to definite MS over a relatively short period of time, and not the range of patients or locations they should be applied to such as other places in the world without advanced MRI technology or with "atypical" patient populations or clinical presentation. The importance of spinal cord or corpus callosum lesions on MRI has not been emphasized, and no evidence has been provided for the accuracy of "Two or more MRI-detected lesions consistent with MS plus positive CSF" as evidence for DIS in 2 of the 5 presenting categories of MS.

In spite of these reservations, the McDonald criteria provided important implications for both patients with suspected MS and their physicians, such as the ability to diagnose MS after a single clinical attack (CIS), the importance of MRI in the diagnosis of MS and the resultant

Table 2
Poser criteria 1983 [26].

	Attacks	Clinical lesions		Paraclinical lesions	CSF Bands or elevated IgG index
Clinically definite MS	2	2			
	2	1	and	1	
Laboratory-supported definite MS	2	1	or	1	+
	1	2			+
	1	1	and	1	+
Clinically probable MS	2	1			
	1	2			
	1	1	and	1	
Laboratory-supported probable MS	2				+

facilitation of access to MRI along with standardization of the performance and interpretation of MRI in the diagnosis of MS [31].

The first revision to the McDonald criteria was published in 2005 [32]. Based on new information obtained, the definition of DIT was modified to a new T2 lesion, compared with a reference scan performed at least 30 (instead of 90) days after the initial clinical event. In addition, the significance of MRI spinal cord lesions was defined: A spinal cord lesion could be considered equivalent to a brain infratentorial lesion or count as one brain lesions to reach the required number of T2 lesions. An enhancing spinal cord lesion was considered to be equivalent to an enhancing brain lesion. While recognizing the usefulness of positive CSF in the diagnosis of PPMS, the 2005 revised criteria indicated that with appropriate MRI findings in the brain and spinal cord, CSF abnormalities were not required for a definitive diagnosis [33]. The 2005 revised criteria resulted in maintaining the high specificity (>90%) of the original McDonald criteria, and achieving higher sensitivity (77%) and accuracy (86%) in the definite diagnosis of MS after the first CIS [34].

Table 3
2001 McDonald diagnostic criteria [27].

Clinical presentation	Additional data needed for MS diagnosis
≥2 attacks; objective clinical evidence of ≥2 lesions	None
≥2 attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: • MRI Or • ≥2 MRI-detected lesions consistent with MS plus positive CSF Or • Await further clinical attack implicating a different site
1 attack; objective clinical evidence of ≥2 lesions	• Dissemination in time, demonstrated by: • MRI Or • Second clinical attack
1 attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	• Dissemination in space, demonstrated by: • MRI Or • ≥2 MRI-detected lesions consistent with MS plus positive CSF And • Dissemination in time, demonstrated by: • MRI Or • Second clinical attack
Insidious neurologic progression suggestive of MS (primary progressive MS)	• Positive CSF And • Dissemination in space, demonstrated by 1)Nine or more T2 lesions in brain, or 2) 2 or more lesions in spinal cord, or 3) 4–8 brain plus 1 spinal cord lesion Or • abnormal VEP associated with 4–8 brain lesions, or with fewer than 4 brain lesions plus 1 spinal cord lesion demonstrated by MRI And • Dissemination in time, demonstrated by MRI Or • Continued progression for 1 year

New evidence and consensus has led to further revision of the McDonald Criteria for diagnosis of MS in 2010 [35] (Table 4), using the Swanton/MAGNIMS (Magnetic Imaging in Multiple Sclerosis) criteria: The definition for DIS was simplified to include at least one T2 lesion in at least two of four key locations: juxtacortical, periventricular, infratentorial, and spinal-cord. Gd-enhancing lesion (a parameter more related to DIT) was no more required for DIS. The criteria for DIT were modified to include any T2 or Gd-enhancing lesion(s) on follow-up scan at any time after the baseline scan, or the simultaneous presence of asymptomatic enhancing and nonenhancing lesions on the same scan (which suggests that they represent 2 or more demyelinating events) regardless of timing [36]. These revised definitions implicate that DIT can be determined on a single baseline MRI scan, and that MS can be diagnosed very early, at the time of CIS presentation. In addition, positive CSF was no longer needed to support the diagnosis of RRMS. The Swanton/MAGNIMS criteria for DIS were found to have similar specificity and higher sensitivity compared with the 2005 McDonald criteria [37,38].

Changes to the MRI definitions of DIS and DIT with each successive revision of the McDonald criteria (Table 5) have resulted in a potentially easier and earlier diagnosis of definite MS while preserving high specificity (thus minimizing misdiagnosis) and increasing sensitivity (to identify previously undiagnosed patients earlier) and accuracy of the diagnosis. The 2010 revisions, which are intended for use in patients with a typical CIS (or insidious neurologic progression suggestive of PPMS), have several other implications [39]: 1) The earlier shift of more and more patients from the category of CIS to a definite diagnosis of MS may affect patient selection for initiation of treatment or for clinical trials and have impact on the prognosis (the "Will–Rogers phenomenon" [40] that is already evident by a lower event rate in recent MS clinical trials that include patients with earlier stage of MS [41] or by increased proportion of patients that convert from CIS to MS with radiologic changes only with no further clinical attacks [40,42]). 2) Daily practice evaluation can be simpler and more efficient by reducing the number of MRI scans required for diagnosis. 3) The sensitivity and specificity of the complete set of the 2010 McDonald criteria have not been fully evaluated yet. Nevertheless, clinicians should be cautious in overemphasizing MRI finding without making a thorough clinical evaluation and careful differential diagnosis [43], as the MRI criteria by themselves do not distinguish between MS and other disorders that can cause similar changes in the brain, and are not sufficient to support a reliable diagnosis of MS. This has been demonstrated in a recent study where 2.4%–7.1% of 168 headache patients between the ages of 10–55 with T2 white matter hyperintensities on a brain MRI met the Barkhof criteria for MS, while 24.4%–34.5% met the more liberal 2010 McDonald criteria [44]. This emphasizes again the importance of clinical judgment and the principle of "no better explanation" in the diagnosis of MS. 4) Similar to the Barkhof–Tintoré criteria, the Swanton/MAGNIMS criteria were developed in centers with special interest in MS and MRI, based on typical and well-defined adult European MS patients. Their sensitivity,

Table 4
2010 McDonald diagnostic criteria [32].

Clinical presentation	Additional data needed for MS diagnosis
≥2 attacks; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
≥2 attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: • ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) Or • Await a further clinical attack implicating a different CNS site
1 attack; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time Or • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; Or • Second clinical attack
1 attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: • ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) Or • Await a second clinical attack implicating a different CNS site; And For DIT: • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time Or • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; Or • Await a second clinical attack
Insidious neurologic progression suggestive of MS (primary progressive MS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index

specificity and reliability may differ in other populations (pediatric MS, subpopulations of other ethnic origin or other atypical clinical presentation) or in the general neurology practice. Although the 2010 McDonald criteria state that the updated definition should serve well for most pediatric patients, they cautious that a single MRI scan is not sufficient to establish either DIS or DIT, particularly in preadolescents with acute disseminated encephalomyelitis (ADEM)-like attacks [35]. 5) Patients with 2010 McDonald MS could comprise a portion of participants in previous clinical trials that assessed the effect of various treatments on CIS. These patients may have different treatment response, natural history and prognosis than the remaining patients with CIS that have not met the 2010 McDonald criteria, which may affect the results and interpretation of previous clinical trials. This also raises the questions whether or not treatments currently approved for CIS are equally effective in the remaining less active CIS population. The new criteria will also affect ongoing clinical trials by introducing the need for post hoc analyses according to the old and new definitions. Furthermore, the new criteria and the associated Will Rogers phenomenon will result in even lower event rate in future clinical trials in MS and CIS, which will make it more difficult to show a statistically significance difference

Table 5
McDonald updates from 2001 to 2010.

	2001	2005	2010
MRI DIS	≥3 of: • ≥9 T2 lesions or ≥1 enhancing lesion • ≥3 periventricular lesions • ≥1 juxtacortical lesion • ≥1 infratentorial lesion 1 cord lesion can replace I brain lesion	≥3 of: • ≥9 T2 lesions or ≥1 enhancing lesion • ≥3 periventricular lesions • ≥1 juxtacortical lesion • ≥1 infratentorial lesion Any number of cord lesions can be included	≥1 T2 lesions in ≥2 of the following areas: • Periventricular • Juxtacortical • Infratentorial • Spinal cord
MRI DIT	≥1 enhancing asymptomatic lesion ≥3 months after CIS onset ≥1 new T2 lesion on a scan obtained ≥3 months after CIS	≥1 enhancing asymptomatic lesion ≥3 months after CIS onset ≥1 new T2 lesion on a scan obtained ≥30 days after CIS	Asymptomatic enhancing and nonenhancing lesions simultaneously present at any time ≥1 new T2 or enhancing lesion on follow-up MRI at any time
CSF to support?	Yes	Yes — in RRMS	No

Abbreviations: CIS — Clinically isolated syndrome; CSF — Cerebrospinal fluid; DIS — Dissemination in space; DIT — Dissemination in time; MRI — Magnetic resonance imaging; RRMS — Relapsing–remitting multiple sclerosis;

between treatment groups. To avoid this possibility, future clinical trials will have to recruit a higher number of patients and change eligibility criteria or use alternate outcome measures.

5. Conclusions

The diagnosis of MS is based on the demonstration of dissemination of lesions in space and in time along with the exclusion of alternative diagnoses. Although this can be made on clinical grounds alone as demonstrated by earlier sets of diagnostic criteria for MS, the recent McDonald criteria emphasize the ability of MRI to support, supplement, or even replace some clinical criteria and enable earlier diagnosis of MS, while maintaining specificity and sensitivity. The simplified MRI criteria for DIS and DIT may also facilitate more uniform and widespread use of imaging in the diagnosis of MS. In order for these criteria to be appropriately translated into the general clinical practice, both neurologists and radiologists reporting MRI results should be educated with understanding the new criteria and their clinical rationale, recognizing their advantages and limitations, and using them correctly.

Despite the incorporation of MRI and other paraclinical evidence into the diagnostic scheme, careful clinical evaluation and judgment, and the principle of "no better explanation" remain the most important aspects of MS diagnosis and should not be replaced by any diagnostic test.

The 2010 McDonald criteria make an important contribution to the diagnostic algorithm of MS, but some questions still remain about the validation of the new DIS and DIT definitions in a wider population of patients seen in daily practice, their sensitivity, specificity and prognostic value in other subpopulations, the status of RIS and its place in the criteria, and the role of other MRI abnormalities (gray matter lesions, brain atrophy and normal-appearing white matter) or new biomarkers in the diagnosis of MS. Future revisions of the current criteria should address these issues, based on new data and large cohort studies.

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