Turkish Journal of Neurology

Turk J Neurol 2025;31(3):255-269
Doi: 10.55697/tnd.2025.500

INVITED REVIEW

Redefining multiple sclerosis: 2024 McDonald diagnostic criteria

Hazal Ceren Manazoğlu[1], Murat Kürtüncü[2]

[1]Department of Neurology, Health Sciences University, Ümraniye Training and Research Hospital, İstanbul, Türkiye
[2]Department of Neurology, İstanbul University, İstanbul Faculty of Medicine, İstanbul, Türkiye

ABSTRACT

This review aimed to provide a comprehensive summary of the 2024 McDonald diagnostic criteria, emphasizing key innovations in cerebrospinal fluid and imaging biomarkers, and to discuss their clinical relevance in improving diagnostic accuracy and reducing misdiagnosis. The present review synthesized evidence from recent prospective studies, expert panel recommendations, and updated diagnostic algorithms. Each revision was critically appraised in light of supporting literature, including validation studies of biomarkers such as the kappa free light chain index, central vein sign, and paramagnetic rim lesions. The implications of these updates were evaluated for various clinical scenarios, including clinically isolated syndrome, radiologically isolated syndrome, and atypical presentations. The inclusion of the optic nerve as a fifth topographic region for dissemination in space and the recognition of the kappa free light chain index as a quantitative alternative to oligoclonal bands for dissemination in time represent major advancements. Central vein sign and paramagnetic rim lesions have been endorsed as supportive imaging biomarkers with high specificity for multiple sclerosis (MS), although they remain optional. In cases with lesions in four or five topographic regions, a diagnosis can now be made without evidence of dissemination in time. Furthermore, radiologically isolated syndrome with compatible lesions and at least one supportive biomarker may fulfill MS diagnostic criteria. For primary progressive MS, ≥2 characteristic spinal cord lesions may suffice as objective evidence in place of cerebrospinal fluid findings. The 2024 McDonald criteria refine MS diagnosis by integrating validated fluid and imaging biomarkers, enabling earlier and more accurate diagnosis. These updates are expected to significantly impact clinical decision-making, particularly in atypical presentations and differential diagnoses.

Keywords: Central vein sign, kappa free light chain index, multiple sclerosis, paramagnetic rim lesions, 2024 McDonald criteria.

First introduced in 2001, the McDonald criteria marked a paradigm shift in multiple sclerosis (MS) diagnosis by formally integrating magnetic resonance imaging (MRI) into the diagnostic framework.[1] Subsequent revisions in 2005, 2010, and 2017 further emphasized the central role of MRI and incorporated cerebrospinal fluid (CSF) oligoclonal bands (OCB) as additional diagnostic markers.[2-4] Collectively, these updates have progressively enabled earlier and more accurate diagnoses.

The diagnostic criteria for MS have evolved in parallel with advances in clinical practice, neuroimaging, and biomarker research. Until recently, the cornerstone of MS diagnosis rested on demonstrating demyelinating events at two or more anatomically distinct locations within the central nervous system (CNS) and at different time points, named dissemination in space (DIS) and dissemination in time (DIT).[2] However, the long-standing paradigm that both DIS and DIT are mandatory prerequisites for diagnosis is now undergoing fundamental revision.

The most recent revision of the McDonald criteria, announced at the ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis) Congress in 2024 and expected to be published in 2025, introduces a more biologically

Correspondence: Murat Kürtüncü, MD. İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Nöroloji Anabilim Dalı, 34093 Fatih, İstanbul, Türkiye.
E-mail: kurtuncum@gmail.com
Received: June 16, 2025 **Accepted:** June 23, 2025 **Published online:** September 15, 2025
Cite this article as: Manazoğlu HC, Kürtüncü M. Redefining multiple sclerosis: 2024 McDonald diagnostic criteria. Turk J Neurol 2025;31(3):255-269. doi: 10.55697/tnd.2025.500.

TABLE 1
Novel diagnostic features introduced in the 2024 McDonald criteria

Diagnostic features
• DIS now requires typical lesions in at least two of five regions: optic nerve, juxtacortical/intracortical, periventricular, infratentorial, and spinal cord
• Meeting both DIS and DIT criteria remains sufficient for MS diagnosis, consistent with the 2017 McDonald criteria
• DIS combined with positive CSF findings, either OCB or elevated kFLC index, allows MS diagnosis without additional DIT evidence.
• In typical clinical presentations, detecting lesions in ≥4 topographic regions is sufficient for MS diagnosis, without the need for CSF biomarkers or DIT.
• In patients with typical symptoms and one region involved, MS diagnosis is possible if either 6 CVS-positive lesions or 1 PRL is present, along with DIT or positive CSF biomarkers (OCB or κFLC).
• In progressive MS, the presence of ≥2 spinal cord lesions is sufficient to meet the DIS criterion, reflecting the disease's spinal cord predilection.

DIS: Dissemination in space; DIT: Dissemination in time; MS: Multiple sclerosis; CSF: Cerebrospinal fluid; OCB: Oligoclonal bands; κFLC: Kappa free light chain; CVS: Central vein sign; PRL: Paramagnetic rim lesion.

grounded diagnostic approach (Table 1).[4] In this new framework, biomarkers in blood and CSF, optic nerve involvement (assessed via MRI and optical coherence tomography [OCT]), and radiological biomarkers such as the central vein sign (CVS) and paramagnetic rim lesions (PRLs) play a central role (Figure 1).[5-11] Notably, the reclassification of radiologically isolated syndrome (RIS) as MS under certain conditions represents a fundamental conceptual shift.[5]

One of the most notable changes is the broader acknowledgment of biological markers as sufficient evidence of temporal dissemination. While the 2017 criteria already allowed a diagnosis of MS in patients fulfilling DIS and showing CSF OCB positivity, the 2024 criteria extend this approach by explicitly formalizing the use of both OCB and elevated kappa free light chains (kFLC) as acceptable alternatives to radiological DIT. Although DIT remains a supportive finding, its absence does not preclude the diagnosis when robust biological markers are present.[4,12,13]

Another major update is the expansion of DIS to include the optic nerve as the fifth anatomical region, alongside periventricular, juxtacortical/cortical, infratentorial, and spinal cord regions. This change is expected to facilitate earlier diagnosis in patients who present with optic neuritis.[14] Importantly, the 2024 McDonald criteria allow a diagnosis of MS when DIS is demonstrated in any four of the five anatomical regions, even in the absence of DIT, provided that clinical symptoms are characteristic.[4]

The redefinition of RIS also represents critical advancement. Previously, RIS was a radiological diagnosis that required a clinical event to confirm the diagnosis of MS. The 2024 criteria allow MS diagnosis in RIS patients if DIS is demonstrated along with biological markers or at least six CVS-positive lesions.[5]

Finally, the same diagnostic framework is applied to all MS subtypes, including primary progressive MS (PPMS). A diagnosis of PPMS requires at least one year of retrospectively or prospectively determined continuous clinical progression, along with at least two of the following: *(i)* ≥1 T2-hyperintense lesions in typical MS brain regions (periventricular, juxtacortical/cortical, or infratentorial); *(ii)* ≥2 T2-hyperintense lesions in the spinal cord, which also fulfill the DIS criterion; or *(iii)* presence of OCBs or elevated kFLC index. These criteria ensure diagnostic accuracy by incorporating both clinical and paraclinical evidence.[15]

REDEFINING DISSEMINATION IN SPACE AND TIME

The concepts DIS and DIT were initially defined based on classical clinical observations and were supported by imaging techniques and biomarkers, providing more objective and earlier diagnostic opportunities.[5,16] The 2024 McDonald criteria aim to establish a biologically grounded, specific, and sensitive approach to MS diagnosis by introducing fundamental changes to the definitions of both DIS and DIT.[4,5]

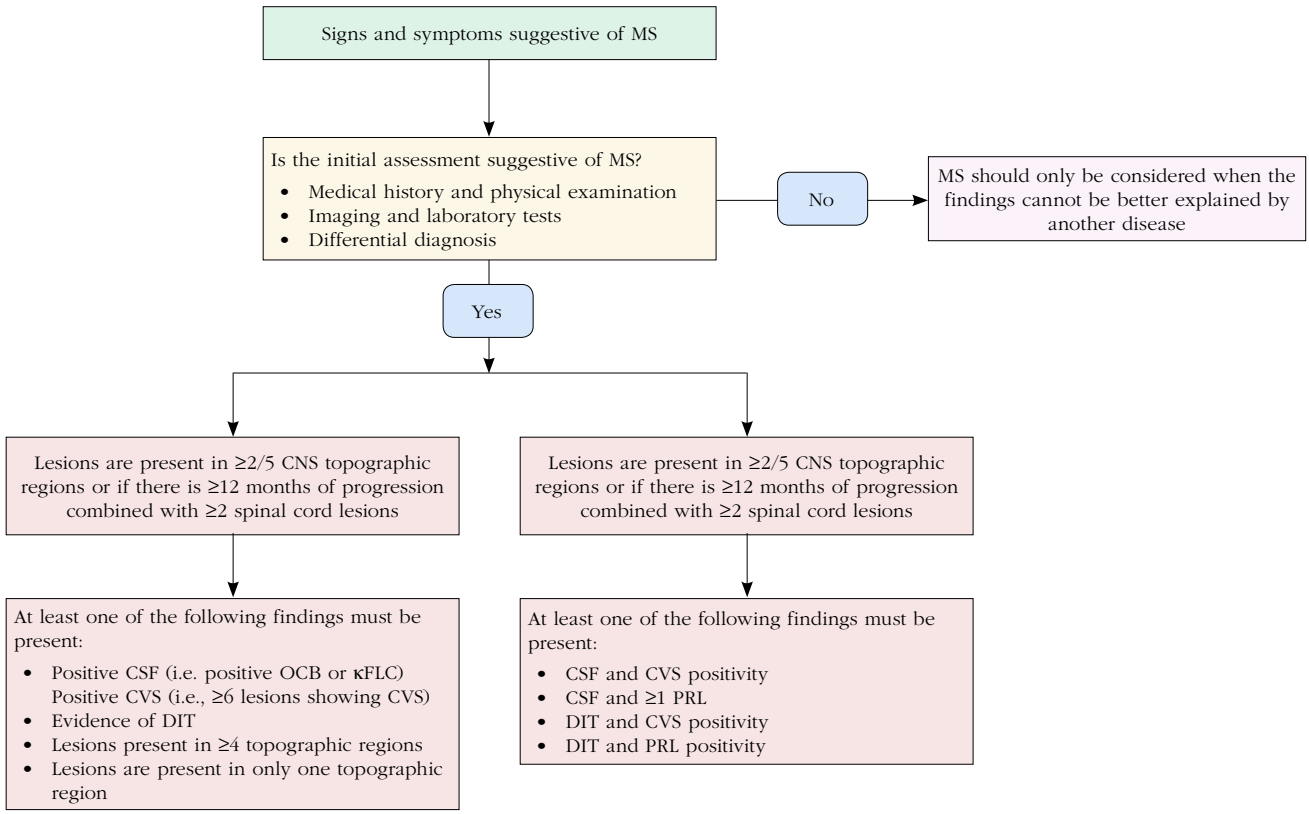

Figure 1. Diagnostic flowchart for MS based on the 2024 McDonald criteria.

MS: Multiple sclerosis; CNS: Central nervous system; CSF: Cerebrospinal fluid; OCB: Oligoclonal bands; κFLC: Kappa free light chains; CVS: Central vein sign; DIT: Dissemination in time; PRL: Paramagnetic rim lesion.

EXPANSION OF DISSEMINATION IN SPACE CRITERIA: OPTIC NERVE AS THE FIFTH TOPOGRAPHIC REGION

The 2024 McDonald criteria incorporate the optic nerve as a fifth anatomical region for establishing DIS, alongside the previously defined regions: juxtacortical/intracortical, periventricular, infratentorial, and spinal cord (Figure 2).[17] This revision facilitates earlier diagnosis, particularly in patients presenting with optic neuritis, which constitutes the first clinical symptom in approximately 25 to 35% of individuals with clinically isolated syndrome (CIS).[14,17] This is supported by findings from a Turkish cohort, where specific clinical and radiological features in patients with optic neuritis were found to predict conversion to MS.[18]

At the initial diagnostic evaluation of a patient with optic neuritis, in addition to brain and spinal cord MRI, optic nerve MRI should be prioritized, as it is essential for both confirming MS diagnosis and excluding alternative pathologies. Magnetic resonance imaging provides the advantage of direct morphological visualization of optic nerve lesions, thereby facilitating differential diagnosis by ruling out other causes of optic nerve damage, such as compressive or infiltrative pathologies.[19] In cases where optic nerve MRI is not feasible, OCT or visual evoked potential (VEP) may be employed based on institutional resources and expertise.

INCORPORATING OPTICAL COHERENCE TOMOGRAPHY AND VISUAL EVOKED POTENTIALS IN THE DIAGNOSTIC EVALUATION OF OPTIC NERVE

In eyes with a prior history of optic neuritis, optic nerve involvement is observed in 73 to 100% of cases; in asymptomatic eyes, reported rates vary between 9% and 72%.[14,17,19] In the absence of alternative etiologies, VEP demonstrating prolonged P100 latency or significant inter-eye asymmetry can be considered evidence of optic nerve involvement.[14] Optical coherence

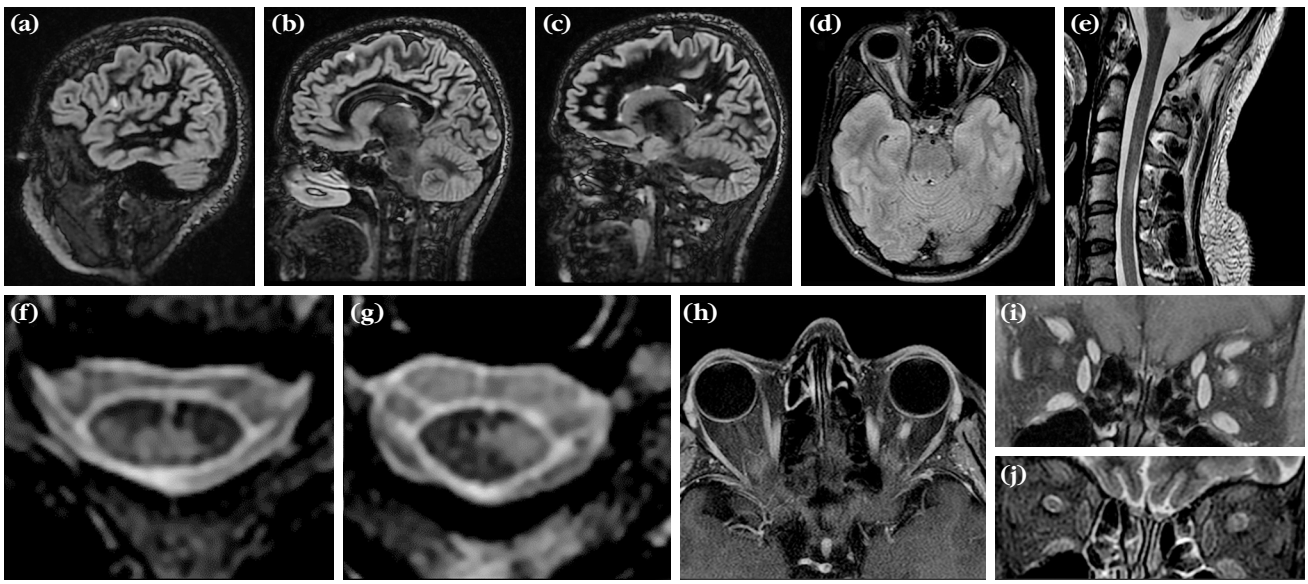

Figure 2. Magnetic resonance imaging sequences demonstrate the five central nervous system topographic regions for dissemination in space. At least one lesion must be present in two or more of the five CNS regions. **(a)** Cortical lesion on sagittal DIR, **(b)** juxtacortical and periventricular lesions, **(c)** infratentorial and periventricular lesions, **(d)** right optic nerve lesion infratentorial lesion on axial FLAIR, **(e)** sagittal T2-weighted image showing a spinal cord lesion, **(f, g)** Axial STIR images of cervical spinal cord lesions in different segments. **(h, i, j)** left optic nerve involvement, **(h, i)** contrast enhancement of the anterior left optic nerve on fat-saturated T1-weighted image; **(j)** enhancement and thickening of the left optic nerve on coronal STIR image.

CNS: Central nervous system; FLAIR: Fluid-attenuated inversion recovery; STIR: Short tau inversion recovery.

tomography findings, such as reduced peripapillary retinal nerve fiber layer (pRNFL) thickness or thinning of the ganglion cell-inner plexiform layer (GCIPL), may also serve as supportive evidence, particularly when measurements fall below normative thresholds or show marked inter-eye asymmetry. In the acute or subacute phase of optic neuritis, however, OCT findings can be confounded by optic disc edema, potentially leading to artifactual increases in pRNFL thickness. Therefore, diagnostic interpretation based on OCT is more reliable outside the acute phase (Figures 3, 4).

Optical coherence tomography further aids in the characterization of optic nerve involvement by enabling longitudinal assessment of edema resolution and atrophy progression. It also facilitates differential diagnosis by distinguishing unilateral

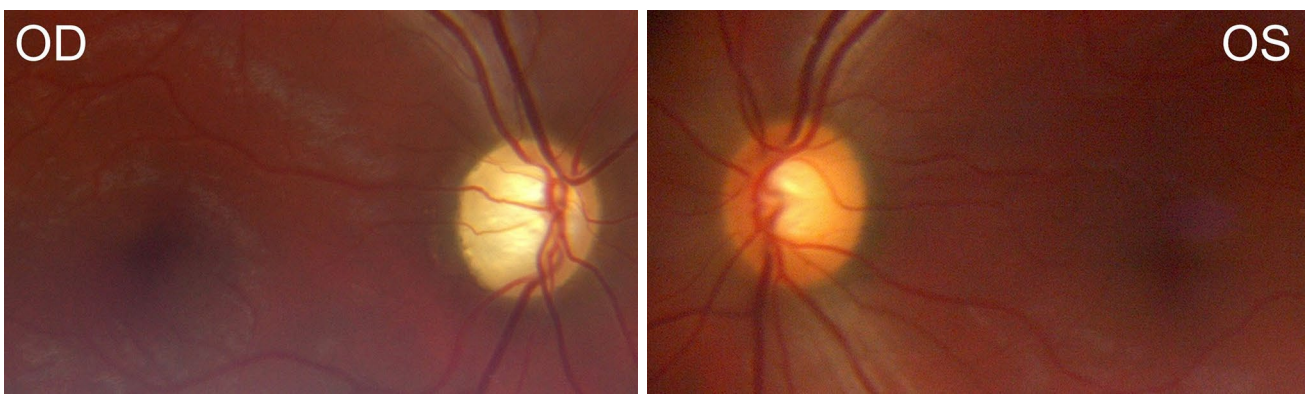

Figure 3. Fundus photographs demonstrating optic disc atrophy in the right eye (OD) of a 37-year-old male patient who had optic neuritis 15 years ago. The right optic disc appears pale and sharply demarcated, consistent with chronic optic atrophy, whereas the left optic disc (OS) appears normal in color and contour.

OD: Oculus dexter; OS: Oculus sinister.

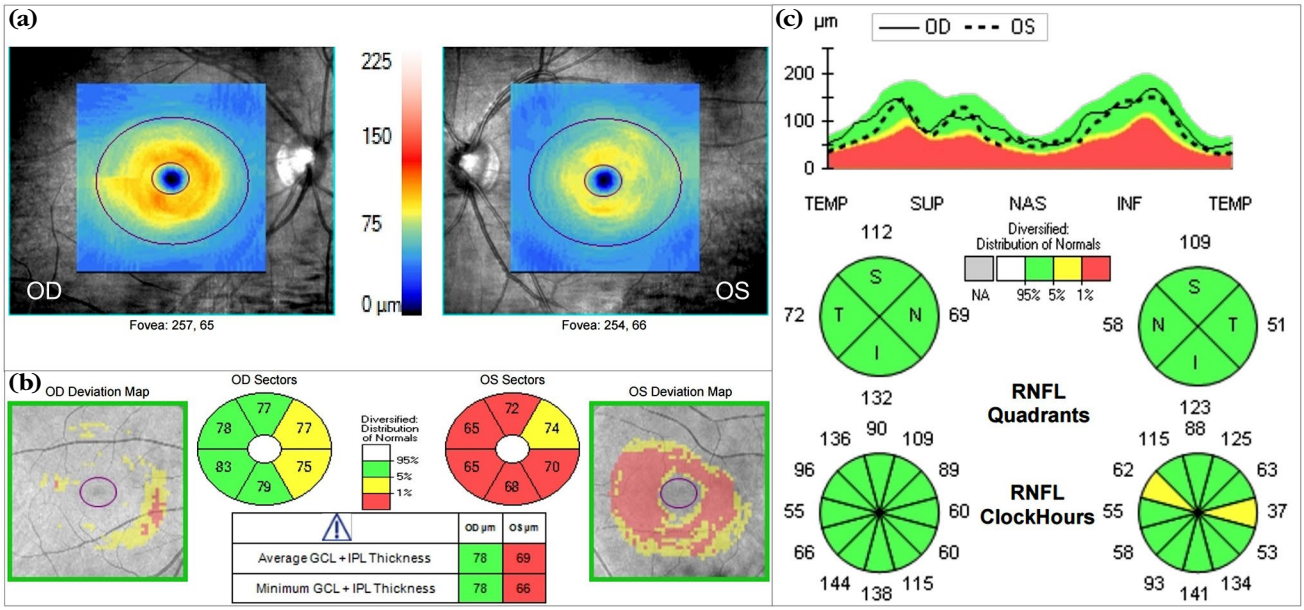

Figure 4. Optical coherence tomography findings in a 23-year-old female patient with a history of left eye optic neuritis, nine months after the acute episode. **(a)** Retinal thickness heat maps show marked thinning of the macular GCIPL in the left eye (OS) compared to the right (OD). **(b)** Ganglion cell layer deviation maps and sectoral thickness plots reveal clear ganglion cell layer + inner plexiform layer atrophy in the left eye, with borderline thinning in the left eye. **(c)** Mild peripapillary RNFL loss across two clock-hour sectors, whereas the right eye remains within normal limits.

GCIPL: Ganglion cell-inner plexiform layer; OD: Oculus dexter; OS: Oculus sinister; RNFL: Retinal nerve fiber layer.

versus bilateral involvement and differentiating optic neuritis from noninflammatory conditions such as macular edema, retinal vascular pathology, or vitamin B12 deficiency. An inter-eye difference of ≥5 µm in pRNFL thickness and ≥4 µm in GCIPL thickness is generally considered pathological.[20] Ganglion cell-inner plexiform layer measurements are considered more reliable in identifying prior optic neuritis. In MS, optic nerve damage typically presents with localized and asymmetric thinning, while neuromyelitis optica spectrum disorder (NMOSD) often displays more severe, bilateral pRNFL loss.[12] Similarly, if present, optic disc edema in MS tends to be focal, whereas myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) usually presents with diffuse and prominent disc swelling.[21]

The timing of evaluation in cases with acute optic neuritis is critical for the appropriate interpretation of diagnostic tests. Visual evoked potentials are most sensitive when performed shortly after symptom onset, but their diagnostic utility may decline over time due to remyelination or progressive axonal loss (Figure 5).[14] In contrast, OCT becomes more informative when conducted at least three months after symptom onset, as this allows time for resolution of acute edema and more accurate quantification of retinal thinning.[14] It is important to note that in cases with bilateral symmetric optic nerve or chiasmal involvement, the diagnostic sensitivity of these modalities, particularly OCT, may be significantly reduced.[19]

REDEFINITION OF DISSEMINATION IN TIME BASED ON DISSEMINATION IN SPACE

In the 2024 McDonald criteria, the definition of DIT has evolved from a reliance solely on conventional imaging findings toward a more biomarker-centered approach.[4] In the 2017 criteria, DIT was demonstrated by one of the following: the simultaneous presence of both gadolinium (Gd)-enhancing (active) and nonenhancing (chronic) lesions on the same MRI scan or the appearance of new Gd-enhancing or new T2 hyperintense lesions on the follow-up MRI. While these findings remain valid, DIT is no longer a mandatory prerequisite for diagnosis in the 2024 criteria. In patients with typical clinical presentations, the presence of characteristic lesions in four or more of the five topographic

Protocol / Run	N75 (ms)	P100 (ms)	N145 (ms)	P100 (µV)
R - VEP				
1.1 O1 - Fz	78	115	147	4,4
1.2 Oz - Fz	80	113	151	7,1
1.3 O2 - Fz	79	112	141	2,9
L - VEP				
1.1 O1 - Fz	96	127	159	2
1.2 Oz - Fz	94	126	154	4,7
1.3 O2 - Fz	93	127	163	3,5

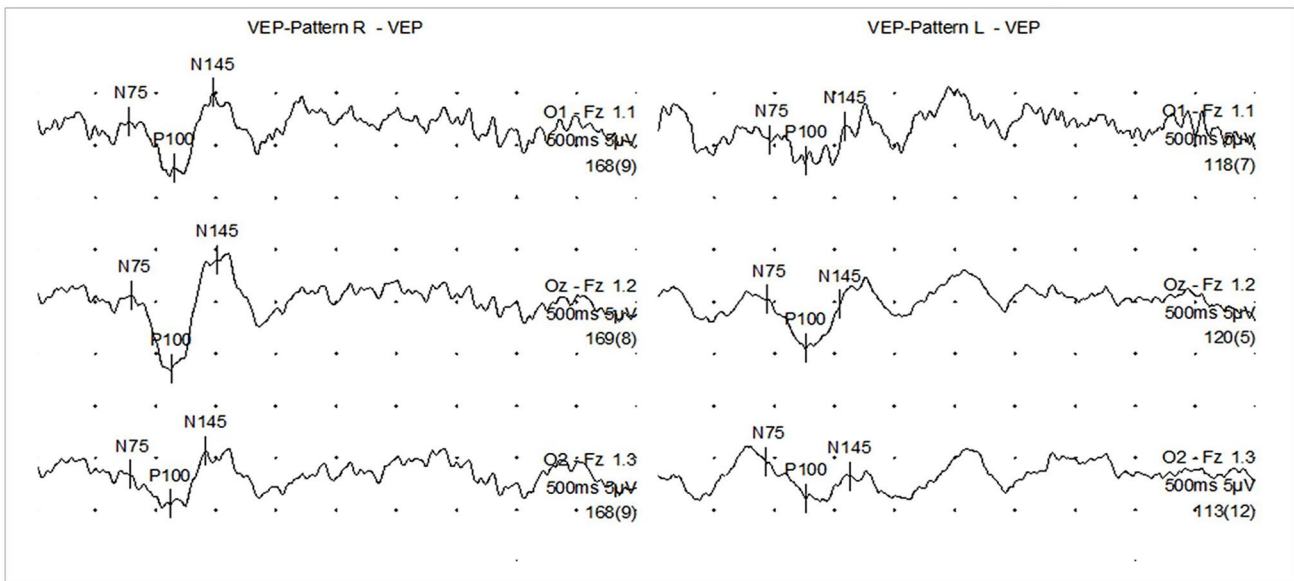

Figure 5. Pattern VEP recordings of a patient one month after left optic neuritis. The top panel displays delayed P100 latency on the left side (L-VEP: 126-127 msec) compared to the right eye (R-VEP: 112-115 msec). The waveform plots in the lower panel further confirm prolonged P100 latencies and reduced amplitudes on the left side.

VEP: Visual evoked potential; L-VEP: Left visual evoked potential; R-VEP: Right visual evoked potential.

regions (periventricular, juxtacortical/cortical, infratentorial, spinal cord, or optic nerve) now permits a diagnosis of MS without the need for separate evidence of DIT.[4]

DEMONSTRATING DISSEMINATION IN TIME THROUGH CEREBROSPINAL FLUID BIOMARKERS: OLIGOCLONAL BANDS AND THE KAPPA FREE LIGHT CHAIN INDEX

While positive CSF OCBs were already accepted as evidence of DIT in the 2017 criteria, the 2024 revision recognizes the kFLC index as an independent and equivalent CSF biomarker for DIT.[13] The diagnostic value of CSF OCBs in supporting DIT has also been highlighted in a recent national study, where their presence was associated with earlier diagnosis and greater lesion burden on MRI.[22] Although OCB testing has long served as a reliable marker in MS diagnosis, it is a qualitative technique that depends heavily on interpreter expertise and lacks interlaboratory standardization.[5] In contrast, the kFLC index provides a quantitative, objective measure derived from the differential concentration of kFLCs in CSF and serum, offering faster analysis and more reproducible results.[23]

Kappa free light chains are immunoglobulin light chain fragments secreted by clonally expanded B cells within the CNS. Intrathecal B-cell activity has traditionally been assessed using OCBs. In contrast, kFLC quantification provides a standardized and quantitatively

interpretable surrogate for assessing intrathecal immunoglobulin synthesis.[5]

The kFLC index is calculated as the ratio of CSF to serum kFLC concentration, adjusted by the albumin quotient, and reflects intrathecal synthesis. Studies demonstrated that the kFLC index had comparable sensitivity and specificity to OCB detection and that it could serve as a valuable diagnostic tool, particularly in early disease stages.[6] Within the framework of the 2024 MS diagnostic criteria, the kFLC index has been formally acknowledged as a valid biomarker for DIT, functioning either as an alternative to or complement to OCB in clinical practice.

IMAGING BIOMARKERS AND MAGNETIC RESONANCE IMAGING CRITERIA

Changes in magnetic resonance imaging criteria

Imaging continues to be one of the most fundamental paraclinical tools in diagnosing MS. With the 2024 revision of the McDonald criteria, significant structural and biological modifications have been made to the MRI-based diagnostic framework. These changes aim to enhance both the sensitivity and specificity of diagnosis and to improve diagnostic reliability, particularly in patients with atypical clinical presentations or at higher risk of false-positive diagnoses.

With the 2024 criteria, the role of MRI has evolved beyond merely documenting the number and location of lesions, and imaging biomarkers have become central to the diagnostic process. In particular, MRI findings such as the CVS and PRLs are distinct for MS and aid in differentiating it from other white matter diseases (Figure 6).[24-26] These findings offer a more selective and reliable MS diagnosis than conventional MRI lesion analyses.

The detection of CVS in six or more lesions achieved diagnostic specificity rates exceeding 90%, and the presence of PRLs further strengthened the differentiation between MS and its mimics.[8] Moreover, advancements in 3T and 7T magnetic field strength have enabled more precise detection of cortical lesions, thereby improving diagnostic reliability.[27]

Central vein sign

Perivenular demyelination is a hallmark pathological feature of MS, and the CVS refers

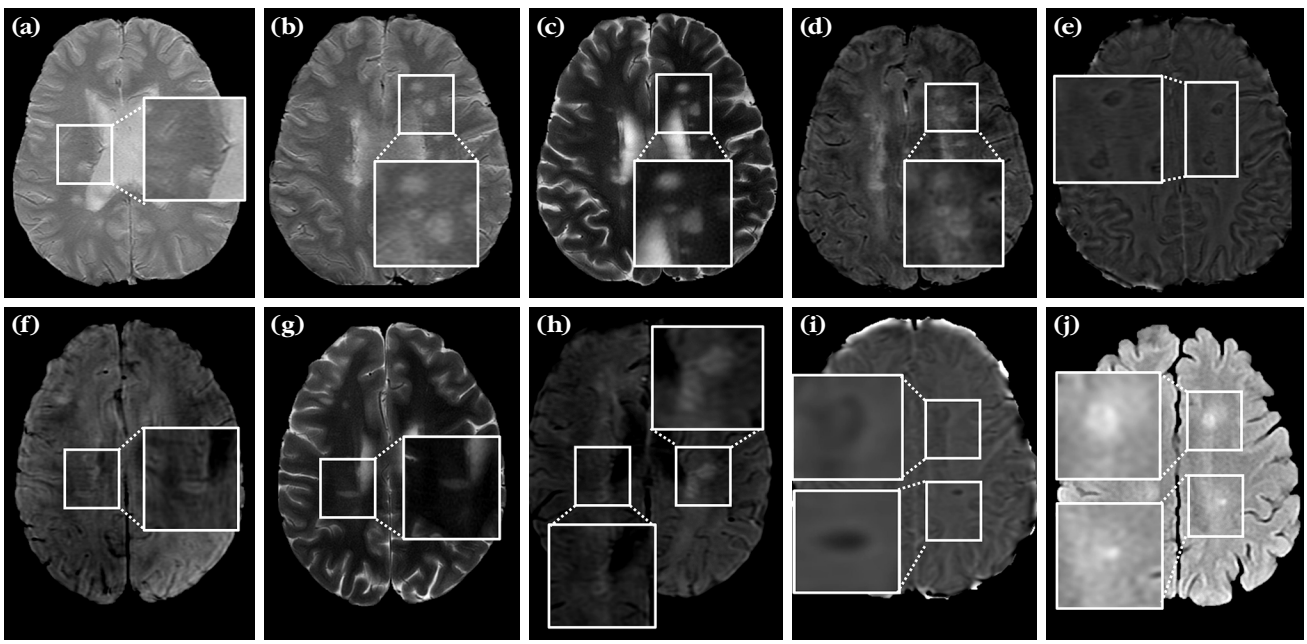

Figure 6. Central vein sign and PRL in MS and RIS. **(a, b)** Central vein sign visualized on 1.5T SWI, **(c)** Dot sign and CVS observed on 3T T2-weighted T2W, **(d)** Dot sign on 3T SWAN sequence, **(e)** Paramagnetic rim lesion on 3T SWAN-filtered phase image, **(f, g)** Central vein sign in RIS on 3T SWAN and T2W sequences, respectively, **(h)** Central vein sign on 3T SWAN, **(i, j)** Paramagnetic rim lesions visualized on 3T SWAN and corresponding FLAIR images.

PRL: Paramagnetic rim lesion; MS: Multiple sclerosis; RIS: Radiologically isolated syndrome; SWI: Susceptibility-weighted imaging; CVS: Central vein sign; T2W: T2-weighted; SWAN: Susceptibility-weighted angiography; FLAIR: Fluid-attenuated inversion recovery; 3T: 3 Tesla; 1.5T: 1.5 Tesla.

to a thin venous structure, typically observed at the center of white matter lesions (Figure 6).[23] Optimal detection of CVS relies on advanced imaging techniques such as three-dimensional (3D) fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted imaging (SWI), and merged FLAIR/T2-weighted sequences, which enhance visualization of perivenular anatomy and help distinguish MS-specific lesion patterns.[25]

Studies have demonstrated that the presence of CVS in at least 40% of white matter lesions confers up to 90% diagnostic specificity for MS.[5,8,25,28] particularly when differentiating MS from its mimics such as NMOSD, MOGAD, and small vessel ischemic disease. Although spinal cord involvement is less well studied, one report and corresponding pathological evidence suggest the presence of CVS in MS spinal cord lesions.[5,29]

T2-weighted MRI sequences, which exploit blood's magnetic properties to produce hypointense signals, remain the optimal modality for venous visualization.[30,31] When combined with FLAIR images, veins appear as hypointense dots or lines traversing the lesions. Several protocols, including FLAIR 3D echo planar imaging, SWI, and susceptibility-weighted angiography-venule imaging, have proven effective for CVS assessment.[32] Importantly, not all T2-hyperintense lesions should be evaluated for CVS. Evaluation should focus on nonconfluent demyelinating lesions larger than 3 mm since smaller lesions may produce false negatives, particularly on 1.5T or 3T scanners.[33]

For CVS assessment, lesions must be visible in at least two perpendicular planes, with the central hypointense vein visualized as a dot in one and a line in the orthogonal plane. The North American Imaging in Multiple Sclerosis Cooperative consortium has proposed specific radiological criteria for CVS identification, which aid standardized clinical implementation (Table 2).[5,32]

In patients with MS, CVS-positive lesions are significantly more prevalent compared to controls.[8,24] However, MOGAD patients may also exhibit CVS-positive lesions, with up to 33% positivity reported in some studies,[25] underscoring the importance of interpretive caution (Table 3).

Incorporating CVS into diagnostic algorithms can substantially improve diagnostic accuracy. For instance, adding at least one CVS-positive lesion to MRI-based DIS evaluation increases diagnostic accuracy from 78 to 86%, comparable to the diagnostic gain achieved with OCB positivity.[5] Multicenter studies have consistently shown high specificity (85 to 95%) and good sensitivity

TABLE 2
Magnetic resonance imaging features used to define the CVS according to North American Imaging in Multiple Sclerosis Cooperative[32]

MRI Feature	Description
Appearance	A thin hypointense line or small dot
Visibility	Visible in at least two orthogonal planes (must appear as a thin line in at least one plane)
Vein size	The visible vein should have a small diameter (<2 mm)
Vein position	The vein should wholly or partially traverse the lesion
Lesion centering	The vein should be located centrally within the lesion

CVS: Central vein sign; MRI: Magnetic resonance imaging.

TABLE 3
Recommended diagnostic scenarios involving CVS in the 2024 McDonald diagnostic criteria

Recommendation
• In patients with typical clinical presentations and lesions in at least one topographic region, the presence of ≥6 CVS-positive lesions supports the diagnosis of MS
• In cases with only one topographic region involved, the diagnosis of MS can be established if CVS positivity is combined with CSF biomarker evidence (e.g., OCB or elevated κFLC index)
• CVS positivity is not mandatory for diagnosis but serves as a valuable supportive marker that enhances diagnostic specificity

CVS: Central vein sign; MS: Multiple sclerosis; CSF: Cerebrospinal fluid; OCB: Oligoclonal bands; κFLC: Kappa free light chain.

(74 to 92%) for CVS-based MS diagnosis.[23-25,32] Two complementary thresholds have emerged: demonstrating at least six CVS-positive lesions or ≥40% CVS-positive white matter lesions.[4,8,24,25] Both strategies yield diagnostic performance comparable to OCB-based criteria.

The CVS is particularly useful in differentiating asymptomatic MS activity from nonspecific white matter lesions in older patients with vascular comorbidities.[28] Though no studies have evaluated whether treatment changes based on CVS status improve outcomes, its utility in guiding clinical decisions, particularly in cases with low lesion burden, is gaining recognition. In patients with fewer than six lesions, a predominance of CVS-positive over CVS-negative lesions may favor an MS diagnosis.[25]

Paramagnetic rim lesions

The 2024 MS diagnostic criteria have elevated the significance of PRLs as supportive imaging biomarkers (Table 4). Paramagnetic rim lesions can be identified using advanced MRI techniques, including SWI and quantitative susceptibility mapping, and are detected in approximately 50% of patients with MS.[34] On the contrary, PRLs are rarely observed in MS mimics such as vasculitis, NMOSD, and MOGAD, and the presence of even a single PRL can substantially increase diagnostic specificity (Figure 6).[34]

Histopathologically, PRLs represent chronic active lesions characterized by iron-laden microglia/macrophages at the lesion periphery, reflecting ongoing inflammation and smoldering demyelination.[34] On MRI, these lesions appear as hypointense rims surrounding T2-hyperintense lesions. In a large multicenter study, the presence of at least one PRL yielded a diagnostic specificity of 99.7% for MS or CIS, although sensitivity remained low at 24%.[34] This limited sensitivity underscores their use as a complementary marker rather than a primary diagnostic criterion.

Paramagnetic rim lesions are particularly valuable in diagnostic scenarios requiring high specificity, such as in older patients or those with migraine and vascular comorbidities, in whom misinterpretation of white matter changes may lead to diagnostic uncertainty.[34] Unlike CVS, PRLs are not a mandatory component of the 2024 criteria but serve as supportive evidence, especially when DIS or DIT cannot be sufficiently demonstrated on MRI.[4] For instance, in patients with typical clinical presentations and lesions confined to a single topographic region, the presence of at least one PRL, combined with either evidence of DIT or positive CSF biomarkers (OCB or kFLC index), supports a diagnosis of MS (Table 4).[4]

While PRLs contribute meaningfully to diagnostic accuracy, particularly by differentiating MS from age-related white matter changes or small-vessel occlusion, their absence does not preclude diagnosis. Thus, their use should be context-dependent and integrated with other diagnostic features to avoid overreliance on a single imaging marker.[24,26]

Recommended magnetic resonance imaging acquisition protocols

The 2024 McDonald diagnostic criteria emphasize a structured and comprehensive MRI protocol to demonstrate DIS and DIT and reliably detect newly recognized imaging biomarkers, such as the CVS and PRLs, as summarized in Table 5.[27]

FLUID BIOMARKERS IN DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

For many years, the diagnosis of MS was based primarily on clinical findings and MRI, with biomarkers playing only a limited role. However, in recent years, various biomarkers obtained from CSF and blood samples have been shown to reflect the disease process at a biological level. With the introduction of the 2024 McDonald criteria, these biomarkers have now been positioned more

TABLE 4
Diagnostic application of PRLs in the 2024 McDonald criteria

Recommendation
• In patients presenting with typical symptoms and only one DIS topography, the presence of ≥1 PRL combined with CSF biomarker positivity is sufficient for diagnosis
• In RIS patients, if DIS criteria are met along with PRL positivity and CSF biomarker positivity, an MS diagnosis can be made even without clinical symptoms

PRLs: Paramagnetic rim lesions; DIS: Dissemination in space; CSF: Cerebrospinal fluid; RIS: Radiologically isolated syndrome; MS: Multiple sclerosis.

TABLE 5
Recommended MRI acquisition protocols for MS diagnosis according to the 2024 McDonald criteria

Parameters	Recommendation
Scanner field strength	≥1.5 T, preferably 3 T
Slice thickness and resolution	3D acquisition with ≤1 mm isotropic voxels; if not available, use 2D with ≤3 mm slice thickness (ideally 1.5 mm) and ≤10% slice gap
Core brain MRI sequences	Axial 3D-FLAIR: For white matter lesions and DIS
	Axial T2-weighted: To assess lesion characteristics
	Sagittal T2-FLAIR (± fat suppression): For periventricular and corpus callosum lesions
	Post-Gadolinium T1-weighted (3D MPRAGE preferred): For detecting DIT via contrast-enhancing lesions
Optional brain sequences	DIR or PSIR: For enhanced cortical lesion detection
	SWI or combined FLAIR/T2: For CVS and PRL
Spinal cord MRI	Sagittal T2-weighted and PD/STIR: Slice thickness ≤3 mm Post-Gadolinium T1-weighted sagittal: For enhancing lesions Axial T2-weighted: To confirm lesion localization and tract involvement
7T MRI	Not recommended for routine clinical use; offers superior spatial resolution but requires expert interpretation and lacks standardized criteria

T: Tesla; FLAIR: Fluid-attenuated inversion recovery; DIS: Dissemination in space; T2: T2-weighted; MPRAGE: Magnetization-prepared rapid gradient ECHO; DIT: Dissemination in time; PSIR: Phase-sensitive inversion recovery; SWI: Susceptibility-weighted imaging, PRL: Paramagnetic rim lesion, PD: Proton density, STIR: Short tau inversion recovery; MRI: Magnetic resonance imaging.

centrally within diagnostic algorithms. Their contribution has become critical, particularly in cases where DIT cannot be demonstrated during the diagnostic process.

EMERGING BIOMARKERS IN BLOOD

Neurofilament light chain (NfL) is a biological marker of axonal damage and can be measured in CSF and serum. Elevated levels of serum NfL (sNfL) have been associated with disease activity, including relapses, the formation of new lesions, and ongoing neurodegenerative processes in MS. With advancements such as the single molecule array (Simoa) technology, highly sensitive quantification of sNfL has become feasible, enabling its use as a noninvasive biomarker for clinical monitoring.[23] Importantly, high sNfL levels have been observed even in patients with CIS or RIS, suggesting a predictive value for future conversion to MS.[23] Furthermore, sNfL has been shown to correlate with baseline MRI lesion burden and to predict new T2- or Gd-enhancing lesions, as well as brain and spinal cord atrophy and future disability progression.[23] Its levels also decrease in response to effective treatments, which makes it useful for treatment monitoring.[23]

Glial fibrillary acidic protein (GFAP), on the other hand, reflects astrocytic damage and is particularly elevated in progressive forms of MS, suggesting its association with neurodegeneration rather than inflammation.[23] When interpreted alongside sNfL, GFAP provides additional diagnostic and prognostic information, especially in distinguishing between relapsing and progressive MS phenotypes.[23] Elevated serum GFAP levels correlate with Expanded Disability Status Scale scores and lesion burden, particularly in patients with PPMS.[23]

A recent study demonstrated that the combination of elevated sNfL and GFAP levels improved the predictive value for MS diagnosis even in patients who did not meet DIS/DIT criteria at baseline.[6] These findings support the integration of sNfL and GFAP into the diagnostic framework for early MS, particularly in challenging cases.

THE IMPORTANCE OF BIOMARKERS IN THE DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS AND OTHER DEMYELINATING DISEASES

Diagnosing MS requires careful differentiation from antibody-mediated diseases such as NMOSD and MOGAD, where AQP4 (aquaporin-4) immunoglobulin G (IgG) or MOG-IgG antibodies are diagnostic. In contrast, these antibodies are typically negative in classical MS, where biomarkers like OCBs and the kFLC index are often

positive.[35] Additionally, spinal cord lesions tend to be short-segment in MS, whereas longitudinally extensive lesions are more typical of MOGAD and NMOSD.[35]

In clinical practice, the following combinations are particularly informative for differential diagnosis. Positive OCB or elevated kFLC in CSF, elevated sNfL, and negative AQP4/MOG antibodies favor MS. The presence of MOG-IgG antibodies, along with often borderline or negative OCB in CSF, favors MOGAD. Positive AQP4-IgG antibodies, typically negative OCB, and longitudinally extensive spinal cord lesions favor NMOSD.

SUBTYPE-SPECIFIC CONSIDERATIONS

Accurate identification of the different clinical subtypes of MS is critically important for diagnosis and determining appropriate treatment strategies. The 2024 diagnostic criteria adopt a more comprehensive and biologically grounded diagnostic approach for all clinical forms of MS, particularly regarding the diagnosis of PPMS.[4]

Updated criteria for primary progressive multiple sclerosis

The primary progressive disease course is observed in approximately 10 to 15% of patients with MS.[15] The PPMS diagnostic criteria were first proposed in 2000.[36] They required evidence of disease progression over at least 12 months, the presence of OCBs in CSF, and demonstration of DIS on MRI.[36] This approach was maintained in the 2017 MS diagnostic criteria, where separate diagnostic requirements were deemed necessary for PPMS and RRMS.[2]

However, this separate diagnostic protocol often led to confusion and diagnostic delays in clinical practice. With the 2024 diagnostic criteria, it is planned to eliminate this distinction and adopt the same diagnostic framework for both primary progressive and relapsing MS.[4] Regardless of the initial disease course, a unified diagnostic algorithm will be applied to all MS subtypes. This approach supports the view that the pathophysiology of MS is based on shared mechanisms. Early inflammatory demyelinating lesions and a similar distribution of CSF biomarkers in relapsing and progressive forms have reinforced this unified perspective.[15] A multicenter study demonstrated that the diagnostic algorithm developed for relapsing MS in the 2017 McDonald criteria could also be successfully applied to patients with PPMS.[15] Specifically, by expanding the DIS criteria, such as including the optic nerve as a fifth region or allowing ≥2 spinal cord lesions as alternative evidence, the sensitivity for PPMS diagnosis increased to over 95%. At the same time, specificity was maintained at 95%.[15]

Under the revised criteria, PPMS diagnosis still requires at least 12 months of clinical progression, along with ≥2 supportive findings such as typical brain lesions, ≥2 spinal cord lesions (fulfilling DIS), or positive CSF biomarkers.[27] This change facilitates earlier diagnosis and treatment initiation, especially in the early stages of the disease.

Diagnostic criteria for secondary progressive multiple sclerosis

Secondary progressive MS (SPMS) represents the progressive phase of relapsing MS, in which the disease gradually evolves into a nonrelapsing, steadily worsening course. Secondary progressive MS is often diagnosed retrospectively once clear clinical progression becomes evident. However, delayed diagnosis can hinder timely therapeutic decisions and increase the disease burden.

Recent efforts have focused on establishing objective criteria based on clinical assessment, imaging, and fluid biomarkers to enable earlier identification of SPMS. In patients suspected of having SPMS, elevated levels of NfL and GFAP in the CSF or serum, along with spinal cord lesions and cerebral atrophy on MRI, may be interpreted as indicative of progression, potentially prompting earlier intervention.[23]

Nevertheless, challenges persist in the clinical diagnosis of SPMS. The Expanded Disability Status Scale is usually not sensitive to capturing subtle progression. Therefore, more sensitive functional assessments such as the Multiple Sclerosis Functional Composite, Nine-Hole Peg Test, and 25-Foot Walk are increasingly being used to monitor disability progression more precisely.[27]

The integration of advanced neuroimaging, fluid biomarkers, and digital technologies (including wearable devices) is expected to support the development of hybrid diagnostic and monitoring models. These systems aim to provide continuous, objective, and individualized assessment of disease activity and progression in clinical practice.

Diagnosis of radiologically isolated syndrome

Radiologically isolated syndrome refers to individuals with MRI findings characteristic of MS

but without clinical symptoms.[37] It is increasingly recognized as the earliest detectable stage of MS in some individuals. Long-term observational studies show that approximately 19% of individuals with RIS develop clinical MS within two years, 35% within five years, and 51% within 10 years.[4]

According to the RIS diagnostic criteria proposed in 2023, RIS can be diagnosed when demyelinating lesions are observed in at least three topographic regions of the CNS (periventricular, cortical/juxtacortical, infratentorial, or spinal cord).[37] In cases with ≤2 topographic regions, the diagnosis of RIS may still be considered if two out of the following three supportive criteria are present: *(i)* CSF OCB positivity, *(ii)* presence of spinal cord lesions, or *(iii)* fulfillment of DIT per the 2017 McDonald criteria.[37]

The 2024 revision of the McDonald criteria introduces a significant conceptual shift by allowing individuals with RIS to receive an MS diagnosis under specific conditions. An MS diagnosis can be formally established if typical lesions are detected in at least two CNS topographies and any of the following are present: positive CSF OCBs or kFLC index, presence of ≥6 CVS-positive lesions, or MRI evidence of DIT.[4] This reclassification of RIS acknowledges its role within the MS disease spectrum and promotes earlier recognition and treatment in high-risk individuals. Importantly, it enables a shift from a purely radiological designation to a diagnosis grounded in biological and imaging evidence. It also reflects a broader transformation in MS diagnostics, from reliance on clinical syndromes to integrating advanced biomarkers and neuroimaging features. The key diagnostic pathways and criteria for RIS within the 2024 MS diagnostic framework are summarized in Figure 7.

Diagnostic recommendations for pediatric-onset multiple sclerosis

It is recommended that anti-MOG IgG testing using cell-based assays be performed in children under 12 who present with new-onset CNS demyelination.[4] In children aged ≥12 years, anti-MOG IgG testing is recommended only if the clinical presentation is atypical MS; it is not recommended for those who present with a clinical picture typical of MS.[4] In patients presenting with acute disseminated encephalomyelitis-like syndrome, the MS diagnostic criteria should only be applied if a second clinical attack typical of MS or new T2-hyperintense lesions in a characteristic

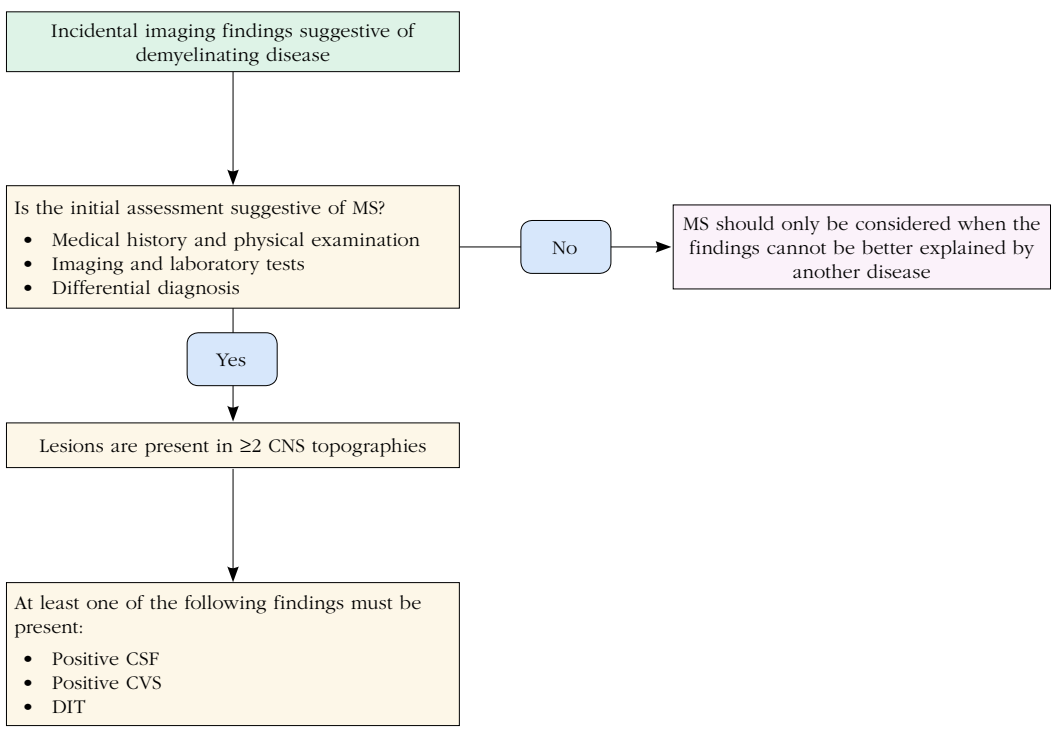

Figure 7. Radiologically isolated syndrome diagnostic flowchart in the 2024 McDonald criteria.

MS: Multiple sclerosis; CNS: Central nervous system; CSF: Cerebrospinal fluid; CVS: Central vein sign; DIT: Dissemination in time.

MS topography occur at least 90 days after the initial event.[4] These distinctions are crucial to avoid misdiagnosis in atypical presentations and pediatric MS.[4]

Data supporting the application of CVS in pediatric-onset MS remains limited. White matter lesions in children under 12 often appear confluent (coalescent) and thus are generally unsuitable for CVS assessment.[4] However, in adolescents and children aged ≥12 years, the presence of CVS in more than 50% of T2-hyperintense lesions strongly supports the diagnosis of MS.[4]

POTENTIAL NATIONAL CHALLENGES IN THE DIAGNOSTIC PROCESS AND PROPOSED SOLUTIONS

A multidimensional approach should be used to address integrating these criteria into clinical practice, the potential challenges encountered during implementation, and specific recommendations within the context of Türkiye. Implementing the 2024 diagnostic criteria may be hindered by several factors, including limited access to advanced imaging protocols and restricted availability of CSF biomarker analyses. This is consistent with findings from a 2009 national survey, which revealed considerable variability among neurologists in Türkiye regarding the use of CSF OCB testing and the implementation of diagnostic criteria in clinical decision-making.[38] Variability in MRI acquisition protocols could compromise the reliable assessment of newly incorporated imaging biomarkers such as CVS and PRLs. Although sequences such as 3D FLAIR, SWI, double inversion recovery, short tau inversion recovery, and phase-sensitive inversion recovery are recommended, their widespread use remains limited across many centers in Türkiye. To address these barriers, the adoption of standardized MRI reporting systems and the strategic referral of patients to centers equipped with advanced imaging capabilities are critical for ensuring the effective use of imaging biomarkers in routine clinical practice.

In conclusion, the 2024 MS diagnostic criteria represent a comprehensive evolution from a purely clinical and imaging-based model to a multidimensional framework integrating biological and radiological data. Effective implementation requires interdisciplinary collaboration, education, and systemic support to ensure optimal patient outcomes.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Contributed to the study design, data collection, analysis and interpretation of data, literature review, writing of the manuscript, and preparation of materials and references: H.C.M.; Contributed to the study conception, design, supervision, interpretation of data, and critical revision of the manuscript. Both authors reviewed and approved the final version of the manuscript: M.K.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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