Classification, diagnosis, and differential diagnosis of multiple sclerosis

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Purpose of review
The increasing availability of effective therapies for multiple sclerosis as well as research demonstrating the benefits of early treatment highlights the importance of expedient and accurate multiple sclerosis diagnosis. This review will discuss the classification, diagnosis, and differential diagnosis of multiple sclerosis.

Recent findings
An international panel of multiple sclerosis experts, the MS Phenotype Group, recently revised the multiple sclerosis phenotypic classifications and published their recommendations in 2014. Recent research developments have helped improve the accuracy of multiple sclerosis diagnosis, especially with regard to differentiating multiple sclerosis from neuromyelitis optica spectrum disorders.

Summary
Current multiple sclerosis phenotypic classifications include relapsing-remitting multiple sclerosis, clinically isolated syndrome, radiologically isolated syndrome, primary-progressive multiple sclerosis, and secondary-progressive multiple sclerosis. The McDonald 2010 diagnostic criteria provide formal guidelines for the diagnosis of relapsing-remitting multiple sclerosis and primary-progressive multiple sclerosis. These require demonstration of dissemination in space and time, with consideration given to both clinical findings and imaging data. The criteria also require that there exist no better explanation for the patient's presentation. The clinical history, examination, and MRI should be most consistent with multiple sclerosis, including the presence of features typical for the disease as well as the absence of features that suggest an alternative cause, for a diagnosis of multiple sclerosis to be proposed.

Keywords
classification, diagnosis, differential diagnosis, multiple sclerosis, phenotype

INTRODUCTION

Since the introduction of interferon in 1993, ongoing research has yielded increasing availability of effective options for the treatment of multiple sclerosis. This, in combination with data suggesting the importance of early therapeutic intervention, highlights the critical nature of prompt and accurate multiple sclerosis diagnosis. When patients present with typical signs and symptoms and have imaging that is consistent with multiple sclerosis, the diagnosis can be relatively straightforward. However, when patients do not easily fulfill diagnostic criteria or when atypical clinical or imaging features are present, making the correct diagnosis may prove challenging even for an experienced neurologist. This review will illustrate the application of recent revisions to multiple sclerosis phenotypic classifications as well as the process for consideration of the diagnosis and differential diagnosis of relapsing and progressive forms of multiple sclerosis.

DEFINITIONS, CLASSIFICATION, AND DIAGNOSTIC CRITERIA

Multiple sclerosis is an inflammatory demyelinating disease affecting the central nervous system (CNS), thought to result from the interaction of genetic and environmental factors that remain only partially understood [1,2]. The pathogenesis of multiple sclerosis is also complex and incompletely understood, but the major principles underlying the

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KEY POINTS

- Current multiple sclerosis phenotypic classifications include RRMS, CIS, RIS, PPMS, and SPMS.
- Phenotype modifiers regarding the presence of recent disease activity and progression have been added to further clarify disease status.
- The McDonald 2010 diagnostic criteria for RRMS and PPMS require demonstration of DIS and DIT through consideration of the patient's clinical presentation as well as imaging characteristics.
- Multiple sclerosis is characterized by well defined clinical syndromes and MRI findings; when these are present and atypical features are absent, further diagnostic evaluation may not be necessary.
- The presence of clinical or imaging 'red flags' that are not typical for multiple sclerosis require further investigation as appropriate.

disease seem to be inflammation and neurodegeneration. The previous classification scheme relied on the idea of the existence of distinct phenotypes dominated by either underlying inflammatory (relapsing-remitting) or neurodegenerative (progressive) disease [3]. Research has since demonstrated that axonal and neuronal loss actually begins at the earliest stages of the disease process, resulting in cognitive impairment and other early disability [4–8]. In addition, it is possible for patients with a more progressive clinical phenotype to have evidence of ongoing inflammatory activity either through clinical relapses or new MRI lesions. These distinctions are important on the clinical level as they influence treatment considerations, payer reimbursement, and eligibility for clinical trials. The classification scheme has therefore been recently revised to incorporate these principles [9▪▪].

Classifications and diagnostic criteria

Relapsing-remitting multiple sclerosis

The vast majority of patients with multiple sclerosis initially follow a relapsing-remitting course, defined by acute exacerbations from which they typically completely or incompletely recover, with periods of relative clinical stability in between. An exacerbation, also referred to as a relapse or an attack, is defined by the International Panel on the Diagnosis of multiple sclerosis as 'patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 h, in the absence of fever or infection' [10]. Diagnostic criteria have changed over time, based on the evolution of research and incorporation of technology to aid the diagnostic process, such as studies illustrating the use of MRI to improve diagnostic sensitivity without compromising specificity [11–14]. Application of the most current criteria, commonly referred to as 'McDonald 2010', does appear to result in earlier multiple sclerosis diagnosis compared with previous criteria [15].

Diagnostic criteria are based on a patient's clinical presentation with typical symptoms and signs related to demyelinating lesions, usually accompanied by imaging that is consistent with multiple sclerosis, disseminated in both space and time. Common presenting syndromes include optic neuritis, sensory and/or motor manifestations of myelitis, and brainstem symptoms such as internuclear ophthalmoplegia. Presenting symptoms, the diagnostic process, and differential diagnosis are discussed in the following sections. The caveat to the application of the McDonald diagnostic criteria is that there must be 'no better explanation', meaning that the patient's symptoms, signs, and imaging should not be diagnosed as multiple sclerosis if they are more consistent with an alternative disease process.

Dissemination in space (DIS) refers to the requirement that lesions affect at least two areas of the CNS typically affected by multiple sclerosis. This can be demonstrated clinically, such as in a patient with a prior history of optic neuritis who now presents with a brainstem syndrome. In this case, DIS is satisfied if there is objective clinical evidence of these two separate lesions or if there is objective clinical evidence of one lesion with a reasonable historical account of the other. However, often a patient will present after only a single event, termed a 'clinically isolated syndrome' (CIS). In this case, DIS may be satisfied if the clinician detects evidence for another separate lesion on neurological examination but may also be satisfied with clinical evidence for only one lesion by incorporating the patient's MRI data. MRI criteria for DIS require the presence of at least one T2 lesion in at least two of the four areas of the CNS typically affected by multiple sclerosis: periventricular, juxtacortical, infratentorial, and spinal cord (Table 1). If the patient has a brainstem or spinal cord syndrome, the symptomatic lesion has presumably already been 'counted' and therefore does not count toward application of the MRI criteria for DIS.

Dissemination in time (DIT) refers to the requirement that CNS lesions have developed over time, to reduce the misdiagnosis of monophasic illness as multiple sclerosis. DIT can easily be

Table 1. 2010 McDonald MRI criteria for demonstration of dissemination in space

DIS can be demonstrated by more than one T2 lesion[a] in at least two of four areas of the CNS:
Periventricular
Juxtacortical
Infratentorial
Spinal cord[b]

Reproduced with permission from [10]. CNS, central nervous system; DIS, dissemination in space.
[a]Gadolinium enhancement of lesions is not required for DIS.
[b]If a patient has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the criteria and do not contribute to lesion count.

satisfied clinically in a patient with two clinical attacks, again with objective clinical evidence for both attacks or for one with a reasonable historical account of the other. However, DIT can also be satisfied with a single clinical episode by the application of MRI criteria. On the patient's initial MRI, DIT can be satisfied by demonstration of the presence of both gadolinium-enhancing and nonenhancing lesions on the same scan, as this illustrates that the lesions presumably developed at different points in time. Of note, the enhancing lesion may not be the symptomatic lesion, which has already been 'counted'. In addition, DIT may be satisfied by the development of any new T2 and/or gadolinium-enhancing lesion with reference to the baseline scan, regardless of the time interval between them. MRI DIT criteria are shown in Table 2.

It should be noted that cerebrospinal fluid (CSF) analysis is not a requirement for the diagnosis of relapsing-remitting multiple sclerosis (RRMS) under McDonald 2010. However, it remains an important part of the evaluation for patients in whom the diagnosis is not entirely clear, either to provide support, paraclinical evidence for multiple sclerosis, or investigate other potential explanations for the patient's presentation. Additional laboratory or other testing should be directed by the patient's clinical presentation and whether there remains suspicion for a disease process other than multiple sclerosis. This is further discussed in the section on differential diagnosis.

Table 2. 2010 McDonald MRI criteria for demonstration of dissemination in time

DIT can be demonstrated by:
(1) A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
(2) Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

Reproduced with permission from [10]. DIT, dissemination in time.

Clinically isolated syndrome

The category of CIS was added to the new classification scheme, although the term has been in use for many years both in research and clinical practice. CIS represents a patient's initial presentation with clinical symptoms typical for a demyelinating event. A patient is classified as having CIS when there is clinical evidence of a single exacerbation and the MRI does not fully meet RRMS criteria. From a practical standpoint, there is little distinction in the approach to a patient classified as having CIS compared with RRMS, as multiple studies have now demonstrated that patients with a typical CIS, especially those with brain lesions consistent with multiple sclerosis on MRI, have a high likelihood of going on to meet RRMS criteria in the future [16,17,18▪] and early treatment is effective at preventing additional relapses [19–24]. The presence of oligoclonal bands seems to be important prognostically [18▪,25], and several recent studies have suggested other potential CSF biomarkers as predictors of conversion from CIS to RRMS [26–29]. In addition, an inverse correlation has been noted between vitamin D level at the time of CIS and the likelihood of going on to meet RRMS criteria [30], but whether this is a marker for some other factor or this may be overcome with vitamin D supplementation is not yet known. Ocular coherence tomography (OCT) may also prove to be helpful as a predictor [31]. As additional research relating to predictive factors is completed, it can be incorporated into techniques such as machine-based learning that employs computerized classification algorithms to estimate future exacerbation risk [32]. This technique could potentially help stratify risk in CIS patients to aid the decision process regarding the timing of initiation of disease-modifying therapy.

Radiologically isolated syndrome

As MRI has become increasingly widespread for headache, trauma, and other conditions, abnormalities suggestive of multiple sclerosis have been noted in patients who have not previously experienced clinical symptoms of the disease. The term 'radiologically isolated syndrome' (RIS) was coined in 2009 [33] and has now been added to the revised multiple sclerosis classification scheme. The current formal diagnostic criteria for RIS are based on the initial 2009 publication, shown in Supplementary Table 1, http://links.lww.com/CONR/A31. They require that lesions are ovoid and well circumscribed, not consistent with a vascular pattern, and meet three out of four Barkhof criteria [34]: one gadolinium-enhancing lesion or at least nine

Table 3. 2010 McDonald criteria for diagnosis of multiple sclerosis in disease with progression from onset

PPMS may be diagnosed in patients with:
(1) One year of disease progression (retrospectively or prospectively determined)
(2) Along with two of the following three criteria[a]:
(a) Evidence for DIS in the brain based on at least one T2[b] lesion in at least one area characteristic for multiple sclerosis (periventricular, juxtacortical, or infratentorial)
(b) Evidence for DIS in the spinal cord based on more than two T2[b] lesions in the cord
(c) Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated immunoglobulin G index)

Reproduced with permission from [10]. CSF, cerebrospinal fluid; DIS, lesion dissemination in space; PPMS, primary-progressive multiple sclerosis.
[a]If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the criteria.
[b]Gadolinium enhancement of lesions is not required.

total T2 lesions, one juxtacortical lesion, one infratentorial lesion, and three periventricular lesions. The findings must be incidental, meaning there must be no history of neurological symptoms suggestive of a demyelinating event and the lesions must not account for functional impairment. The lesions must not be better explained by a substance or toxic exposure or another disease process with a specific exclusion for those with extensive white matter disease not involving the corpus callosum. The criteria are likely to be updated in the near future to incorporate McDonald 2010 DIS principles.

In a recent study with an average of 4.4 years of follow-up, 34% of patients developed a first clinical event consistent with multiple sclerosis, although this does not represent the natural history of this classification as the group included patients treated with disease-modifying therapy [35▪]. Younger age, male sex, and the presence of spinal cord lesions were noted to have predictive value. Owing to the lack of availability of evidence, currently there exists considerable variability in management, but many clinicians consider the presence of spinal cord lesions, whether the MRI is changing or lesions enhance with gadolinium to indicate ongoing disease activity, and/or the presence of oligoclonal bands in the CSF in the decision regarding whether to initiate disease-modifying therapy for multiple sclerosis in these patients.

Primary-progressive multiple sclerosis

The primary-progressive multiple sclerosis (PPMS) classification describes patients with progressive decline in neurological function from the time of disease onset. Patients most often present clinically with a progressive myelopathy although they may also present with a progressive cerebellar syndrome or other progressive symptoms as described further. McDonald 2010 criteria require at least 1 year of clinical disease progression as well as at least two of the following: evidence for DIS in the brain (at least one T2 lesion that is periventricular, juxtacortical, or infratentorial), evidence for DIS in the spinal cord (at least two T2 lesions in the cord), or positive CSF (isoelectric focusing of oligoclonal bands and/or elevated immunoglobulin G index). As in RRMS, symptomatic lesions are excluded from the MRI DIS lesion count. These are illustrated in Table 3 and the full McDonald 2010 criteria for both RRMS and PPMS are in Table 4.

Secondary-progressive multiple sclerosis

Secondary-progressive multiple sclerosis (SPMS), defined by gradual progression after an initial relapsing course, occurs in up to 40% of patients by 20 years after the initial event [36]. It is typically characterized by a gradual decline in neurologic functioning, often predominantly involving areas of the CNS previously involved during the relapsing course. The point of transition to SPMS can be difficult to define and is often recognized only in retrospect, at times years after subtle hints of progression first appear [37]. Research regarding potential imaging and laboratory biomarkers that distinguish SPMS from RRMS, better characterize the transition from RRMS to SPMS and even potentially predict the transition from RRMS to SPMS, is underway although each suggested biomarker currently requires further validation prior to clinical use [38–43].

Descriptive modifiers of multiple sclerosis phenotypes

Activity

The MS Phenotype Group recommends yearly assessment of clinical and brain MRI activity in patients with relapsing multiple sclerosis. Clinical activity is defined by relapses and brain MRI activity by the presence of gadolinium-enhancing lesions and/or new or unequivocally enlarging T2 lesions. Because spinal cord MRI activity correlates well with brain MRI activity [44], routine spinal cord MRI surveillance in the absence of clinical findings is not required for activity assessment. Regarding

Table 4. 2010 McDonald criteria for diagnosis of multiple sclerosis

Clinical presentation	Additional data needed for multiple sclerosis diagnosis
At least two attacks[a]; objective clinical evidence of at least two lesions or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack[b]	None[c]
At least two attacks[a]; objective clinical evidence of one lesion	DIS demonstrated by: more than one T2 lesion in at least two of four multiple sclerosis-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or await a further clinical attack[a] implicating a different CNS site
One attack[a]; objective clinical evidence of at least two lesions	Dissemination in time, demonstrated by: simultaneous presence of asymptomatic gadolinium-enhancing and none-nhancing 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[a]
One attack[a]; objective clinical evidence of one lesion (clinically isolated syndrome)	DIS and DIT demonstrated by: For DIS: at least one T2 lesion in at least two of four multiple sclerosis-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or await a second clinical attack[a] implicating a different CNS site For DIT: simultaneous presence of asymptomatic gadolinium-enhancing and none-nhancing 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[a]
Insidious neurological progression suggestive of multiple sclerosis (PPMS)	1 year of disease progression (retrospectively or prospectively determined) along with two of the following three criteria[d]: evidence for DIS in the brain based on at least one T2 lesion in the multiple sclerosis-characteristic (periventricular, juxtacortical, or infratentorial) regions evidence for DIS in the spinal cord based on more than two T2 lesions in the cord positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated immunoglobulin G index)

Reproduced with permission from [10]. If the criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is 'multiple sclerosis' if suspicious, but the criteria are not completely met, the diagnosis is 'possible multiple sclerosis'; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is 'not multiple sclerosis'. CNS, central nervous system; CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; PPMS, primary-progressive multiple sclerosis.

[a]An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 h, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for multiple sclerosis, for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 h. Before a definite diagnosis of multiple sclerosis can be made, at least one attack must be corroborated by findings on neurological examination, visual-evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b]Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least one attack, however, must be supported by objective findings.

[c]No additional tests are required. However, it is desirable that any diagnosis of multiple sclerosis be made with access to imaging based on these criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of multiple sclerosis.

[d]Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in patients with brainstem or spinal cord syndromes.

activity assessment in progressive patients, the Group recommends yearly clinical assessment, although they did not reach a consensus regarding imaging.

The modifier 'active' or 'not active' can be applied to each patient for the specified time interval of assessment. This allows for elimination of the previous classification of progressive-relapsing

multiple sclerosis, which had described patients with progression from onset who also had evidence of inflammatory activity. Such patients can now be classified as PPMS active compared with those with a purely progressive course classified as PPMS not active. Patients who have not had a recent activity assessment can be classified with the modifier 'activity not assessed'.

Progression

A diagnosis of progressive multiple sclerosis does not guarantee that the patient will continue to demonstrate ongoing decline. Some patients progress rapidly, some at a slow and steady rate, whereas others seem to reach a plateau [45]. This currently has implications for clinical trial enrolment, as clinical trials in progressive disease require documentation of recent progression for inclusion. In addition, it will hopefully have implications in the future regarding initiation of disease-modifying therapy for progressive disease and ongoing assessment of its effectiveness. The MS Phenotype Group therefore recommended a modifier regarding the current status of progression in patients with progressive disease, adding the term 'progressing' or 'not progressing' to modify the clinical phenotype. The lack of validated biomarkers for progression necessitate that this yearly assessment is purely clinical, based on patient-reported history and objective findings on clinical examination.

The application of the revised clinical classifications with modifiers is illustrated in Supplementary Figs. 1 and 2, http://links.lww.com/CONR/A31.

SYMPTOMS AND SIGNS SUGGESTIVE OF DEMYELINATING DISEASE AND THEIR DIFFERENTIAL DIAGNOSIS

As described previously, the process of diagnosing multiple sclerosis generally begins with a patient who presents with the acute (relapsing) or insidious (progressive) onset of neurological symptoms. Prior to considering the application of multiple sclerosis diagnostic criteria, the clinician must determine whether the clinical history and examination, imaging, and other available data are consistent with demyelination related to multiple sclerosis. It should be noted that multiple sclerosis is not 'a diagnosis of exclusion' and therefore its diagnosis does not require an exhaustive search to exclude all other potential causes for the clinical presentation. Rather, the diagnosis is based on a constellation of findings that are typical for the disease, with tailored additional diagnostic workup required as an absolute only when atypical features are present. Typical presenting features, as well as those that should raise suspicion for an alternate disease process, termed 'red flags' are reviewed here. Examples are provided in the text and a more detailed list of clinical and imaging red flags developed by the Task Force on Differential Diagnosis in multiple sclerosis are presented in Supplementary Tables 2 and 3, http://links.lww.com/CONR/A31.

Clinical features

Spinal cord syndrome

The most common clinical presentation of multiple sclerosis is symptomatology associated with acute onset of a partial transverse myelitis, typically sensory symptoms consistent with involvement of the dorsolateral cord [46▪]. Depending on the extent of the lesion, symptoms may be unilateral or bilateral, at or below the level of the lesion, which in multiple sclerosis most commonly occurs in the cervical cord. The motor system as well as bladder and bowel function may be impaired. Acute complete transverse myelitis with resulting paraplegia is rare in multiple sclerosis and should prompt consideration of other disorders such as neuromyelitis optica spectrum disorder (NMOSD). Acute myelitis due to multiple sclerosis typically evolves over the course of days and begins to spontaneously recover over the course of a few weeks. Brain MRI is quite helpful as the majority of patients with a brain MRI suggestive of multiple sclerosis accompanying a partial acute transverse myelitis will go on to meet multiple sclerosis diagnostic criteria in the near future [47].

A more insidious onset should prompt consideration of PPMS, which in approximately 80% of cases presents as a progressive myelopathy [48]. In PPMS, motor symptoms such as weakness, spasticity, and difficulty with gait tend to predominate over sensory symptoms. Depending on the remainder of the clinical picture, consideration may also be given to compressive disease, toxic-metabolic causes such as B_{12} or copper deficiency, infection such as human T-cell lymphotropic virus, malignancy, or underlying genetic condition such as hereditary spastic paraparesis [46▪,49▪].

Other than the recommended brain and spinal cord MRI (discussed in further sections), the nature and extent of the diagnostic workup of a spinal cord syndrome should be driven by the clinical presentation. For example, a patient with a history of gastric bypass with insidious symptom onset will certainly require evaluation for vitamin deficiencies whereas a patient with an acute partial transverse

myelitis that spontaneously improves as well as brain MRI suggestive of multiple sclerosis may need no further workup at all. Lumbar puncture is recommended in cases of progressive myelopathy in which multiple sclerosis is suspected given the special role CSF plays in the diagnostic criteria for PPMS.

A suggested algorithm for consideration of a spinal cord syndrome related to possible underlying multiple sclerosis is presented in Supplementary Fig. 3, http://links.lww.com/CONR/A31. Other reported potential causes of transverse myelitis are outlined in Supplementary Table 4, http://links.lww.com/CONR/A31, and of spastic paraparesis in Supplementary Table 5, http://links.lww.com/CONR/A31.

Optic neuritis

The differential diagnosis for suspected optic neuritis is quite broad and outlined in Supplementary Table 6, http://links.lww.com/CONR/A31; however, there are particular features that suggest multiple sclerosis-related optic neuritis as the cause as well as others that suggest alternative processes (Supplementary Table 7, http://links.lww.com/CONR/A31) [50▪]. Optic neuritis due to underlying multiple sclerosis typically presents with acute, unilateral, painful decrease in visual acuity that peaks within a few days and begins to recover within a few weeks [51]. A hyperacute presentation should raise suspicion for a vascular process, whereas a more insidious presentation should raise suspicion for an infiltrative disorder such as neurosarcoidosis, toxic-metabolic process such as B_{12} deficiency, or paraneoplastic syndrome although PPMS may rarely present with gradually worsening vision due to progressive optic neuropathy [48]. Simultaneous bilaterality is possible but uncommon and should raise suspicion for processes such as NMOSD, neurosarcoidosis, or Leber's hereditary optic neuropathy (LHON), especially in the setting of a positive family history. In multiple sclerosis-related optic neuritis, pain with eye movements is typically present and mild to moderate in nature [51]. Painless visual loss should cue consideration of a vascular cause, especially in older patients, or LHON, whereas severe pain is more common in NMOSD. Phosphenes and scintillations may be present [50▪].

Examination typically reveals impairments in acuity, low contrast vision, and color discrimination as well as an afferent pupillary defect [52]. Central scotoma is common and a variety of visual field defects are possible. Funduscopic examination is often normal but optic disc swelling may be seen [53]. Poor recovery, even without steroids, is uncommon in multiple sclerosis [52] and more suggestive of LHON or NMOSD [54]. Neuroophthalmology input, especially in cases in which red flags are present, is often helpful.

Brainstem or cerebellar syndrome

The most common brainstem presentation of multiple sclerosis is diplopia due to internuclear ophthalmoplegia, which may be bilateral, although diplopia may also result from a sixth nerve palsy [55]. Facial weakness or loss of sensation may accompany eye movement abnormalities or occur in isolation. Vertigo may occur due to a lesion anywhere along the vestibular pathways and ataxia may result from a cerebellar lesion [55]. Isolated trigeminal neuralgia as the sole presenting symptom of multiple sclerosis is uncommon. Third nerve palsy or complete ophthalmoplegia are more suggestive of other causes. Persistent hiccups, nausea, or vomiting are suggestive of area postrema lesion due to NMOSD. In relapsing multiple sclerosis as with other syndromes, the onset of brainstem or cerebellar symptoms is over hours to days; hyperacute onset is suggestive of a vascular cause especially if the symptoms are consistent with involvement of a clear vascular territory.

Approximately 15% of patients with PPMS will present with a progressive cerebellar or brainstem syndrome, characterized most prominently by gradually worsening ataxia [48]. They may also have progressive worsening of dysarthria, dysphagia, and, note, diplopia. MRI findings and the presence or absence of red flags will guide the differential diagnosis, which includes toxic/metabolic disturbances, malignancy, infiltrative processes, and others.

An algorithm for the evaluation of a patient presenting with an isolated brainstem syndrome is presented in Supplementary Fig. 4, http://links.lww.com/CONR/A31.

Cognitive impairment

Cognitive impairment is common in all multiple sclerosis phenotypes and begins early in the disease, although it is typically much more prominent in progressive than relapsing multiple sclerosis. Cognitive complaints often accompany other symptoms of multiple sclerosis and may help solidify a diagnosis; however, given their nonspecific nature and lack of association to a particular acute CNS lesion (at least with current standard imaging technique), cognitive symptoms alone without focal neurological symptoms are not usually helpful discriminators in the diagnostic process for RRMS.

PPMS may present with cognitive dysfunction without clear simultaneous focal neurological symptoms and signs, as recently illustrated in a small cohort of Italian patients [56▪]. Several of these

patients had atrophy and initially only nonspecific changes on MRI. They were only subsequently diagnosed with multiple sclerosis after additional testing such as advanced imaging with double inversion recovery revealing cortical lesions, or lumbar puncture was consistent with multiple sclerosis.

Other clinical presentations

There are several other less common clinical syndromes that may be consistent with a first presentation of multiple sclerosis. Cerebral hemisphere lesions, particularly large tumefactive brain lesions, can present as a hemispheric syndrome with symptoms that include aphasia, encephalopathy, and manifestations of increased intracranial pressure, in addition to motor and sensory symptoms. Paroxysmal symptoms are transient, recurrent, stereotyped symptoms such as vibrating or shock-like sensation with neck flexion (Lhermitte phenomenon), tonic spasms, trigeminal neuralgia, or paroxysmal dysarthria. Of note, for paroxysmal symptoms to be applied toward diagnostic criteria, they must be recurrent over at least 24 h. Other less common symptoms include seizures and symptoms related to disorders of thermoregulation or sleep [57] but these are rarely the sole presenting symptom of the disease.

Imaging features

Brain lesions related to multiple sclerosis are typically ovoid, well circumscribed, oriented perpendicularly to the ventricles, and occur in characteristic locations: periventricular, juxtacortical, and infratentorial (Fig. 1a–c) [58]. Spinal cord lesions are also well circumscribed, relatively small (typically two or less vertebral segments in length), occupy less than 50% of the cross-sectional cord area, and often involve the dorsolateral cord [59] (Fig. 1d). Lesions at least three vertebral segments in length are suggestive of NMOSD. Diffuse abnormalities in either the brain or spinal cord, especially in the setting of progressive symptom onset, should raise suspicion for a toxic/metabolic or genetic disorder (Fig. 2). New lesions typically enhance with gadolinium for approximately 6 weeks; enhancement that persists beyond 3 months should prompt consideration of other diagnoses such as sarcoidosis, histiocytosis (Fig. 3a–c), chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (Fig. 4), malignancy, or others relevant to the clinical context. Brain lesion load is on average, less in PPMS than RRMS, although atrophy accumulates more quickly in PPMS than RRMS. Supplementary Table 3, http://links.lww.com/CONR/A31, outlines various imaging red flags and their differential diagnosis.

Differentiating multiple sclerosis from neuromyelitis optica spectrum disorder

One of the most common questions raised by referring physicians to multiple sclerosis specialists is whether a patient has multiple sclerosis or the much less common but potentially more severe inflammatory CNS disease NMOSD. The combination of typical clinical features for NMOSD and testing for antiaquaporin 4 antibodies (neuromyelitis optica immunoglobulin G) will correctly differentiate NMOSD from multiple sclerosis in many cases. However, the existence of seronegative NMOSD and overlap of certain clinical and imaging features with multiple sclerosis may complicate this distinction. Supplementary Table 8, http://links.lww.com/CONR/A31, suggests differentiating features of the two disorders and they are reviewed here.

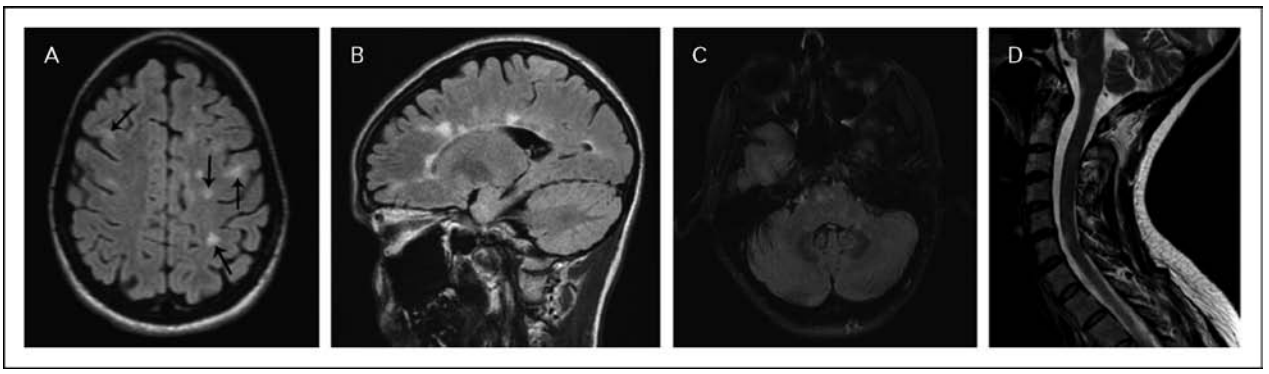

FIGURE 1. Typical appearance of multiple sclerosis lesions on MRI. (a) Axial FLAIR image demonstrating juxtacortical lesions typical for multiple sclerosis. (b) Sagittal FLAIR image demonstrating periventricular lesions, including in the corpus callosum, giving rise to 'Dawson's fingers' appearance. (c) Axial FLAIR images demonstrating infratentorial lesions seen in multiple sclerosis. (d) Sagittal T2-weighted image of the cervical spinal cord demonstrating lesions seen in multiple sclerosis. Reproduced with permission from [58]. FLAIR, fluid-attenuated inversion recovery.

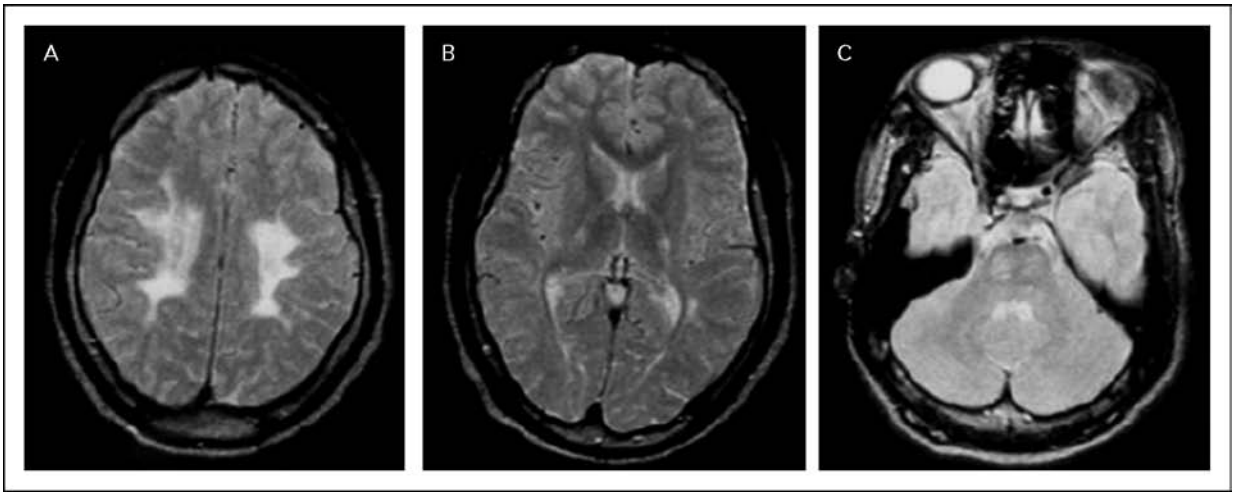

FIGURE 2. (a) Axial T2-weighted image of a 24-year-old female with Krabbe disease (globoid cell leukodystrophy) demonstrating confluent T2 hyperintensity in the bilateral centrum semiovale, centered in the frontoparietal lobes and involving the corticospinal tracts. The patient presented with a 2-year history of worsening spastic paraparesis and symmetrical lower extremity sensory disturbance. (b) Axial T2 and (c) proton-density-weighted images of the same patient showing symmetric hyperintensity in the posterior limbs of the internal capsule and pons, corresponding to the corticospinal tracts. Reproduced with permission from [49▪].

The cardinal clinical presentations of NMOSD are optic neuritis, longitudinally extensive myelitis, and hiccups/nausea/vomiting. Hiccups/nausea/vomiting is rare enough in multiple sclerosis and common enough in NMOSD for this result in a correct NMOSD diagnosis once the symptoms have been recognized to be neurologic in etiology. Myelitis and optic neuritis, however, may present more of a challenge. Unlike in multiple sclerosis, wherein spinal cord lesions are usually small and discrete, in NMOSD, they are classically longitudinally extensive (at least three vertebral segments) and this can help differentiate the two disorders. However, a study from the Mayo clinic group demonstrated the possibility for 'short transverse myelitis' (less than three vertebral segments) in NMOSD, at times incorrectly leading to a diagnosis of multiple sclerosis until patients later presented with a more typical longitudinally extensive lesion or other classic feature of NMOSD [60▪]. Central location of the spinal cord lesion and presence of tonic spasms helped distinguish NMOSD from multiple sclerosis and other disorders in certain cases in this study. Optic neuritis in NMOSD is more likely to be bilateral, posterior, and extensive including involvement of the chiasm [61,62], and result in poor recovery as compared with optic neuritis related to multiple sclerosis [63,64]. OCT may also help in differentiating the two; for example, NMOSD typically results in more retinal nerve fiber and ganglion cell layer thinning than multiple sclerosis, whereas subclinical abnormalities are commonly seen in multiple sclerosis but rare in NMOSD [65▪].

Other clinical features reported in NMOSD include focal brainstem syndromes, syndrome of inappropriate antidiuretic hormone secretion, narcolepsy, or other signs of hypothalamic involvement [66] (Fig. 5), and rarely myeloradiculitis [67] or myopathy with high creatine kinase [68,69], encephalopathy [70,71], or even hydrocephalus [72]. In addition, certain imaging features may help distinguish NMOSD from multiple sclerosis. It was previously thought that NMOSD did not result in abnormalities on brain MRI; however, it has subsequently been shown that patients with NMOSD can in fact have brain MRI abnormalities and some of these can resemble lesions seen in multiple sclerosis [73]. There are several features that may help distinguish them. Longitudinal corticospinal tract lesions (Fig. 6a), extensive hemispheric lesions, cervicomedullary junction lesions, bilateral symmetrical brainstem lesions, and periependymal lesions forming an 'arch bridge' (Fig. 6b) are more common in NMOSD whereas juxtacortical lesions, ovoid lesions perpendicular to the lateral ventricles ('Dawson's fingers'), and asymptomatic gadolinium-enhancing lesions seem to be more common in multiple sclerosis [74▪▪].

Lumbar puncture may also be helpful. CSF in NMOSD often shows high white blood cell count, with neutrophils and eosinophils at times [75], compared with multiple sclerosis wherein more than 50 white blood cells are rare. Oligoclonal bands

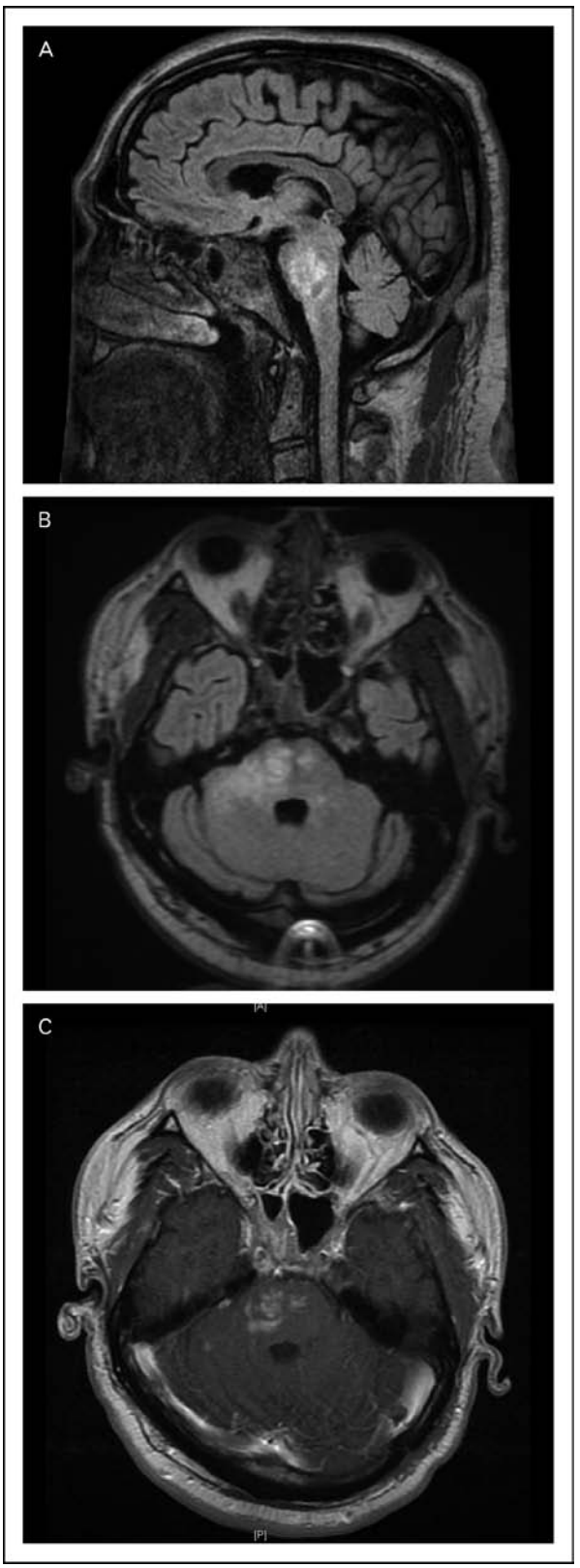

FIGURE 3. (a) Sagittal FLAIR, (b) axial FLAIR, and (c) T1-weighted images with gadolinium in a patient ultimately diagnosed with Erdheim–Chester disease. Reproduced with permission from [58]. FLAIR, fluid-attenuated inversion recovery.

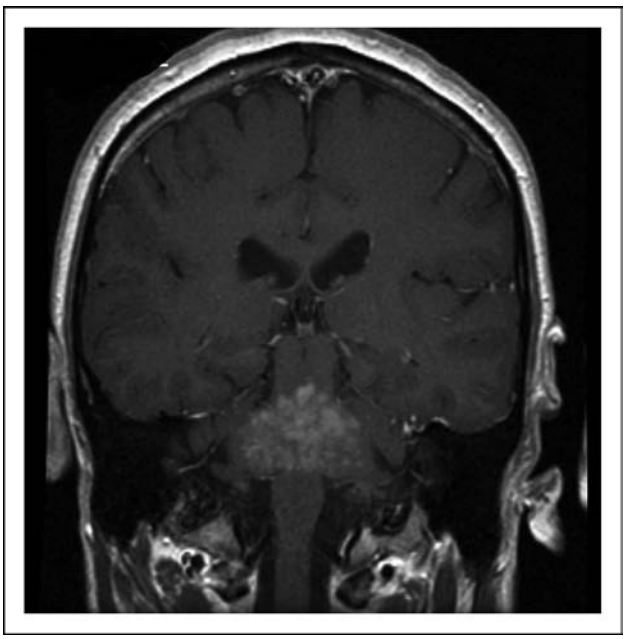

FIGURE 4. Coronal T1-weighted image with gadolinium demonstrating the 'peppered pons' characteristic of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. Reproduced with permission from [78].

are highly associated with multiple sclerosis but are much less common in NMOSD [75,76]. Computer-aided diagnosis employing methods for multimodal data fusion are also being explored and may prove to be powerful diagnostic tools [77].

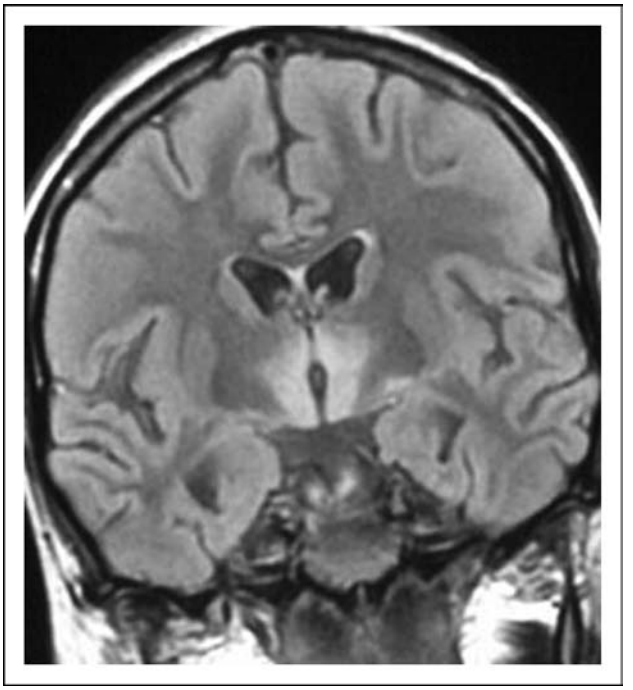

FIGURE 5. Hypothalamic lesions in neuromyelitis optica spectrum disorder. Reproduced with permission from [64].

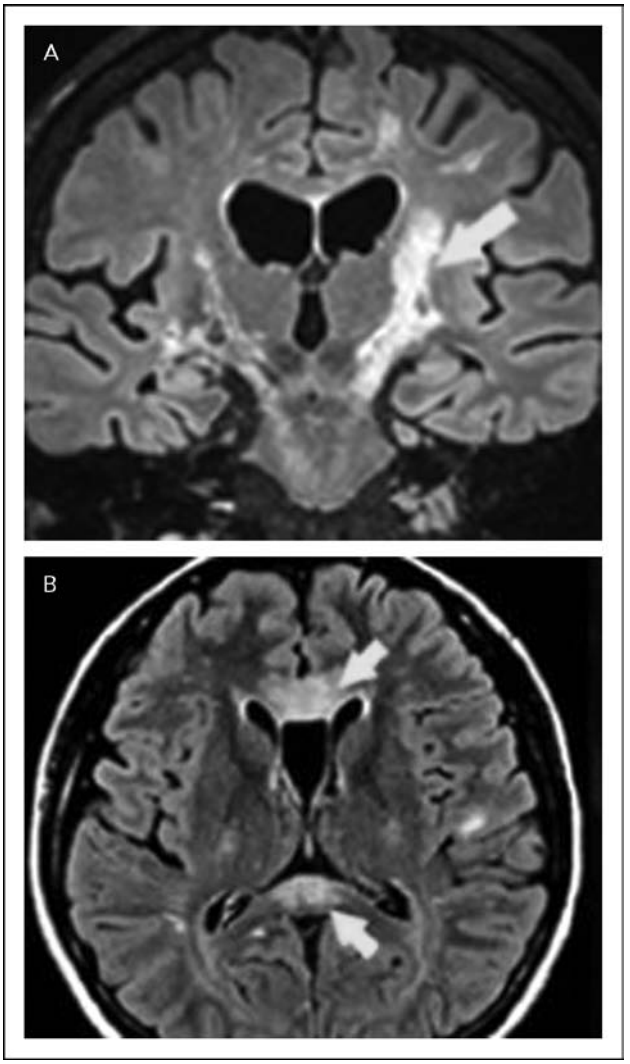

FIGURE 6. Brain MRI features differentiating multiple sclerosis from neuromyelitis optica spectrum disorder. (a) Longitudinal corticospinal tract lesion seen in NMOSD. (b) 'Arch bridge' sign in NMOSD. Reproduced with permission from [74▪▪]. NMOSD, neuromyelitis optica spectrum disorder.

CONCLUSION

As per 2013 revisions to multiple sclerosis phenotypic classifications, patients can be designated as having RRMS, CIS, RIS, PPMS, or SPMS. Modifiers regarding recent disease activity and progression have been added to further clarify current multiple sclerosis disease status.

The diagnostic criteria for RRMS and PPMS require presentation with a syndrome that is typical for demyelination, with demonstration of DIS and DIT. CIS requires a syndrome typical for demyelinating disease and RIS a typical MRI. When the clinical and imaging findings satisfy diagnostic requirements, the most crucial of which is that presenting features are consistent with a multiple sclerosis diagnosis, an exhaustive search regarding differential diagnosis is not necessary. Additional diagnostic testing should be tailored to the patient's presentation, with particular attention to the presence of red flags that suggest a more appropriate alternate diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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