Title: Differential diagnosis of suspected multiple sclerosis: an updated consensus approach

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Summary: Accurate diagnosis of multiple sclerosis (MS) requires careful attention to differential diagnosis - many disorders can mimic the clinical manifestations and paraclinical findings of MS. A collaborative effort in 2008 provided diagnostic approaches to MS and identified clinical and paraclinical findings (so-called “red flags) suggestive of alternative diagnoses. Since then, there has been considerable expansion in knowledge regarding disorders in the differential diagnosis of MS. For example, central nervous system inflammatory disorders that present with syndromes overlapping with MS can increasingly be distinguished from MS with the aid of specific clinical, MRI, and laboratory findings, and studies of people misdiagnosed with MS have provided insights into clinical presentations for which extra caution is warranted. In light of these data, an update to recommended diagnostic approaches to common clinical presentations and key clinical and paraclinical “red flags” is warranted to inform the contemporary clinical evaluation of patients with suspected MS.

Introduction

Diagnosis of multiple sclerosis (MS) requires vigilance for the many disorders that can mimic its varied clinical manifestations and paraclinical findings. Thoughtful consideration of MS differential diagnosis – the concept of "no better explanation" – has remained a fundamental element of MS diagnostic criteria for more than fifty years.[1] A previous panel comprised of experts in the field and organized by the International Advisory Committee on Clinical Trials in MS recommended consensus approaches to MS differential diagnosis and identified key clinical and paraclinical "red flags" suggestive of disorders other than MS.[2] Since its publication in 2008, this paper has remained an informative resource in MS education and clinical care.

Knowledge affecting MS differential diagnosis has increased over the last decade. Contemporary studies have identified disorders most common in people referred to neurologists for suspected MS,[3,4] diagnoses most often misdiagnosed as MS,[5-8] and key findings to aid accurate diagnosis.[9-12] A wealth of data has emerged elucidating the clinical and paraclinical spectrum of central nervous system (CNS) neuroinflammatory disorders that often present with syndromes overlapping those of MS, such as myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (AQP4-IgG+NMOSD), including proposed diagnostic criteria[13,14] and approaches to aid differentiation from MS.[13-17] Recent studies also have suggested expanding the clinical and radiological spectrum of MS.[18-20] The aim of the present paper, prepared by members of the MS Differential Diagnosis Consortium organized by the Americas Committee for Treatment and Research in MS with collaboration of other MS-related organizations (see Appendix page 1), is to provide updated comprehensive consensus recommendations for MS differential diagnosis formulation. We describe approaches to the evaluation of common MS presentations as well as clinical and paraclinical "red flags" suggestive of alternative diagnoses, to inform contemporary education and clinical practice.

Current MS diagnostic criteria were developed and validated in cohorts of patients presenting with clinical syndromes typical for MS. Consequently, confirmation of either a clinically isolated syndrome (CIS)[1] or a progressive course of neurological deficits typical of MS is required for diagnosis of MS.[1,21] Therefore, an optimal approach to MS diagnosis includes careful consideration of the differential diagnosis for these most common location-based clinical presentations, as detailed below. Clinical and paraclinical evaluation for evidence of CNS involvement beyond these syndromes indicating a multifocal disease process is an additional necessary step in diagnostic evaluation. Specific clinical or paraclinical findings, or "red flags", may suggest alternative diagnoses rather than MS. While these findings may be insufficient to entirely exclude MS or confirm an alternative diagnosis on their own, they should prompt further evaluation. Clinical and radiographic findings should guide differential diagnosis formulation to subsequently inform confirmatory blood and cerebrospinal fluid (CSF) testing to minimize the risk of false positive laboratory testing and consequent unnecessary clinical investigations and healthcare cost.[22,23]

Optic neuritis

Clinical considerations

MS-associated optic neuritis (ON)[24] typically manifests as mild-to-moderate unilateral central acuity visual loss, mild retro- or peri-orbital pain that worsens on eye movement, and a normal-appearing or mildly swollen optic disc without hemorrhage or retinal exudates.[24] Impairment in low-contrast acuity and color vision can be disproportionately greater than high contrast visual acuity. Visual loss is typically maximal within two weeks of onset and followed by spontaneous improvement, although some impairment may persist.[25]

The differential diagnosis of ON is broad, and recently published diagnostic criteria for ON[24] aid in its differentiation from optic neuropathies; other ocular disorders such as retinal, uveal and scleral

disease; functional visual loss; and primary headache disorders with peri-ocular pain and/or visual symptoms.[24,26] Many disorders frequently mistaken for ON do not involve the optic nerve,[10,26] and key clinical findings supportive of an optic nerve lesion include unilateral central scotoma with abnormal visual acuity, relative afferent pupillary defect, and impaired color vision (**Figure 1**).[24] The absence of these findings and the presence of other clinical "red flags" suggest an alternative localization (**Table 1**). For instance, stereotyped or recurrent brief episodes of painful visual disturbance with positive visual phenomenon is common in migraine, inconsistent examination findings such as tubular visual field or severe vision loss with lack of an afferent pupillary defect and with intact optokinetic nystagmus suggest the possibility of functional visual loss, and dry eye can cause both visual impairment and discomfort.[10] Distinguishing optic neuritis from other causes of acute visual loss can be difficult and, if available, neuro-ophthalmological evaluation is appropriate in many cases.

Once optic nerve localization is established, attention to the temporal evolution, severity and pattern of impairment, patient demographics, and comorbid conditions help focus differential diagnosis considerations (**Figure 1** and **Table 1**). Hyperacute onset (reaching maximum deficit within several minutes) and/or painless vision loss suggests ischemic optic neuropathy, whereas subacute-progressive visual loss over greater than two weeks is atypical for MS and more common in other inflammatory, neoplastic, and metabolic disorders (**Table 1**).[24] Severe visual loss (e.g. acuity of 20/200 or worse including lack of light perception), bilateral simultaneous or rapidly bilateral sequential visual loss, severe optic disc edema, and/or severe retro orbital pain are all infrequent with MS-associated ON and should prompt consideration of AQP4-IgG+NMOSD, MOGAD,[24,27] infectious disorders, genetic disorders such as Leber's hereditary optic neuropathy, or toxic/nutritional optic neuropathies. Older patients (>50 years) are more likely to present with arteritic and non-arteritic ischemic optic neuropathy than with MS. Conversely, MOGAD should be considered especially in younger patients (e.g <11 years) with suspected ON, particularly when accompanied by features of acute disseminated encephalomyelitis. A

history of malignancy could indicate neoplastic, paraneoplastic, or chemotherapy-induced optic neuropathy.

Paraclinical considerations

Contrast-enhanced fat saturated orbital MRI[28] should be obtained as part of an evaluation of ON. Typical MRI findings for MS-associated ON (**Figure 1**) include short-segment abnormal T2-hyperintensity in any location within the optic nerve, often with contrast-enhancement during the acute phase, and abnormal brain MRI with asymptomatic T2-hyperintense lesions in regions typical for MS. The location and extent of optic nerve involvement on MRI can point toward alternative diagnoses (**Figure 1** and **Table 2**). Bilateral or longitudinally-extensive optic nerve lesions should prompt evaluation for neuroinflammatory disorders other than MS, such as MOGAD and AQP4-IgG+NMOSD.[29] MRI evidence of optic peri-neuritis with optic nerve sheath enhancement is also atypical for MS and can suggest MOGAD, neurosarcoidosis, tuberculosis, or neoplastic infiltration. Long anterior optic nerve segment involvement suggests MOGAD; while posterior optic nerve segment and/or chiasm and optic tract involvement is more typical of AQP4-IgG+NMOSD and neurosarcoidosis.[24,29,30] Normal orbital MRI suggests a non-inflammatory optic neuropathy such as anterior ischemic optic neuropathy, a common mimic of ON especially in older individuals. However, in some cases ischemic optic neuropathy can be associated with optic nerve T2 hyperintensity and enhancement, making differentiation from optic neuritis more challenging and especially reliant upon clinical history and examination.

Paraclincal evaluation utilizing optical coherence tomography (OCT) and visual evoked potential (VEP) can further guide differential diagnosis (**Figure 1**).[24] Severe global peripapillary retinal nerve fiber layer/ganglion cell-inner plexiform layer thinning observed on OCT after a single attack of ON is more typical of AQP4-IgG+NMOSD or MOGAD.[24,31] Superior/inferior or altitudinal involvement is more common in ischemic optic neuropathy versus the temporal quadrant predominant thinning typically

observed in MS. While a prolonged VEP P100 latency with relatively preserved amplitude is typical of MS, severe amplitude reduction without P100 prolongation could indicate AQP4-IgG+NMOSD[32] or non-inflammatory optic neuropathies.

Brainstem or Cerebellar Syndromes

Clinical considerations

Symptoms typical of an MS attack localizing to the brainstem or cerebellum include diplopia, oscillopsia, unilateral facial numbness with or without pain, incoordination, and gait instability (**Figure 2**).[21] Corresponding neurological exam findings can include internuclear ophthalmoparesis (INO), sixth nerve palsy, gaze-evoked nystagmus, ocular ataxia, and limb or gait ataxia.[21,33]

Specific history or neurological exam findings can point toward the varied disorders that can mimic brainstem or cerebellar presentations of MS (**Figure 2** and **Table 1**).[12] Encephalopathy, meningism, features of intracranial hypertension, or systemic signs such as fever or oral and genital ulcers[34] would be especially atypical for MS and suggest alternative inflammatory, infectious, neoplastic, and paraneoplastic disorders (**Table 1**). Hyperacute onset of symptoms, particularly in an older patient (older than 50) with vascular comorbidities suggests ischemia - a common cause of INO[35] or isolated cranial nerve mononeuropathies such as a sixth nerve, fourth nerve, or pupil-involving third nerve palsy. Fatigable bulbar muscle weakness suggest a neuromuscular junction disorder such as myasthenia gravis, which also can mimic INO. Complete gaze palsy; bilateral or multiple cranial nerve involvement;[36] and intractable nausea, vomiting, or hiccups (area postrema syndrome)[37] are key findings suggestive of alternative diagnoses (**Table 1**). Hearing loss, or paroxysmal dysarthria or paroxysmal ataxia can occur in MS but are rare presentations and should prompt consideration of other neurological disorders (**Table 1**).[12,38-41] Trigeminal neuralgia (TN) is associated with MS, yet diagnosis of TN in the absence of other

clinical or MRI findings suggestive of MS should initiate evaluation for evaluation for other causes. Continued symptomatic worsening of an acute brainstem or cerebellar syndrome beyond four weeks is uncommon in MS, and should result in evaluation for alternative inflammatory, neoplastic, or metabolic disorders (**Table 1**).

Paraclinical considerations

MRI findings are especially important for differential diagnosis formulation for patients presenting with brainstem and cerebellar syndromes.[12,42] MS lesions most frequently are located at the surface of the brainstem or the fourth ventricle. Lesions in the cerebral peduncles, paramedian medulla, cerebellar peduncles, and cerebellar white matter are also common in MS. MS lesion morphology is typically round or ovoid, and enhancement on post-gadolinium T1-weighted image is typically nodular or ring-like.[42]

Other MRI lesion location, morphology, and enhancement patterns suggest diagnoses other than MS (**Table 2**).[9,12,42] In particular, symmetric central pontine T2-hyperintensities are atypical in MS and common in small vessel ischemic disease and metabolic disorders.[9,42,43] Large, diffuse or ill-defined T2-hyperintense brainstem lesions should prompt evaluation MOGAD,[44] AQP4-IgG+NMOSD, and infections such as progressive multifocal leukoencephalopathy. Area postrema lesions are characteristic of AQP4-IgG+NMOSD.[37] Contrast enhancement within the brainstem or cerebellum that persists >3 months, appears punctiform or miliary, or demonstrates cranial nerve or extensive and diffuse leptomeningeal involvement suggests inflammatory, infectious, neoplastic, and paraneoplastic diagnoses other than MS (**Table 2**).[9,12,42,45,46]

Myelitis

Clinical considerations

Acute myelitis associated with MS typically presents with mild to moderately severe asymmetric sensory symptoms or deficits and/or accompanying weakness or bladder dysfunction (**Figure 3**). [47] In myelitis caused by MS, maximal deficits typically develop over approximately four hours to three weeks.[48]

Attention to the severity and temporal evolution of symptoms can narrow the differential diagnosis and aid discrimination between inflammatory and non-inflammatory causes of myelopathy.[11,49] A hyperacute severe myelopathy with maximal deficits within a few hours suggests spinal cord ischemia[50] or trauma, although functional neurologic disorder might manifest similarly.[51] Absence of reflexes and flaccid tone can accompany ischemia or trauma, or point toward a peripheral nervous system diagnosis or infectious acute flaccid myelitis.[52] Severe acute myelitis associated with loss of ambulation and neurogenic bladder requiring catheterization without recovery is uncommon in MS and suggests AQP4-IgG+NMOSD, MOGAD, or an infectious or an ischemic disorder.[47,53] MS remains in the differential for an insidious progressive myelopathy (see below) that differs from the acute myelitis typical of an MS attack.[47] However, worsening of acute-onset myelitis beyond four weeks is atypical in MS and should prompt consideration of alternative inflammatory, neoplastic/paraneoplastic, metabolic, vascular, and structural diagnoses (**Table 1**).[48]

Paraclinical considerations

Cervical and thoracic spine MRIs including sagittal and axial T2 weighted and contrast-enhanced T1 images are critical diagnostic tools in the evaluation of acute myelitis (**Table 2**).[28,54] After excluding an extrinsic compressive process, assessment of key features of intrinsic spinal cord lesions including T2-lesion length on sagittal imaging, central vs. peripheral location on axial imaging, and the presence of contrast enhancement and its pattern aid differential diagnosis formuation.[47] MS-associated myelitis typically presents with T2 hyperintense lesions that are short in length (<3 vertebral segments) and peripherally located on axial images within the dorsal or lateral columns. The finding of multiple short-

segment peripherally located spinal cord lesions is strongly suggestive of MS. Acute MS spinal cord lesions usually demonstrate nodular enhancement,[42] but can also present with ring-like enhancement.[55]

Centrally located lesions involving over one-half of the spinal cord cross sectional area or longitudinally-extensive T2-hyperintense lesions (≥3 vertebral segments) should prompt evaluation for diagnoses other than MS.[56] Patients with longitudinally-extensive MRI lesions infrequently develop MS.[57,58] However, coalescence of multiple T2-lesions in patients with MS can appear longitudinally-extensive on sagittal imaging, making close scrutiny of axial images for multiple separate lesions important.[58,59] Conversely, although AQP4-IgG+NMOSD and MOGAD are associated with long lesions, both can also initially present with short segment lesions that can be mistaken for MS.[60,61] Radiographic evolution of lesions over time can also aid diagnosis - MS lesions typically persist whereas complete resolution of T2-hyperintense lesions is associated with MOGAD.[62] Short segments of focal spinal cord atrophy are typical of MS, but long segments of atrophy suggests other disorders.[63] Although lesions from MS can occur in any segment of the spinal cord, involvement restricted to the conus medullaris should prompt consideration of MOGAD.[53,64] Lesions selectively and extensively involving the spinal cord grey matter, the anterior spinal cord or anterior horn cells, or the dorsal or lateral columns, should prompt consideration of alternative diagnoses (**Table 2**).

While contrast enhancement on MRI often supports a diagnosis of inflammatory myelitis, caution is warranted – contrast enhancement is also associated with neoplastic, vascular, and compressive myelopathies. Attention to specific enhancement patterns atypical for MS such as dorsal sub-pial, transverse-band, or persistent (>3 months) enhancement, can help narrow differential diagnosis considerations (**Table 2**).[65,66]

When MRI evidence of a spinal cord lesion is equivocal, somatosensory or motor evoked potentials can aid confirmation of spinal cord pathology. Normal evoked potentials in patients with normal spinal cord imaging should prompt consideration of diagnoses other than myelopathy.

Supratentorial Syndromes

Clinical Considerations

MS can present with a supratentorial syndrome[1] – but rarely, representing 1%-2% of cases of MS in some prospective cohorts.[67,68] Supratentorial presentations can manifest as hemiparesis, hemisensory disturbance, or homonymous visual field defects. Because supratentorial clinical presentations of MS are infrequent, an initial approach to differential diagnosis should be broad, and include evaluation for additional clinical characteristics typical of MS, such as evidence of prior attacks suggestive of ON, myelitis, or common brainstem/cerebellar syndromes.

Although supratentorial by localization, predominant subacute cognitive changes, encephalopathy, or seizures in isolation from other symptoms or neurological findings are atypical for MS, and should prompt consideration of alternative diagnoses (Table 1). Cortical presentations, including encephalopathy or seizures, have been described in MOGAD, often accompanied by symptoms suggestive of extensive cortical and leptomeningeal involvement atypical for MS.[69,70] Cerebral ischemia is an important consideration for supratentorial presentations and a history of hyperacute onset of maximal deficits aids differentiation from demyelination. Other vascular disorders such as evolving central venous sinus thrombosis could also mimic supratentorial presentations of MS.

Paraclinical Considerations

MRI lesions associated with supratentorial presentations of MS are usually in the pre or post-central gyrus, occipital cortex, or extending into the internal capsule. Diffusion restriction can indicate ischemia, but can also be observed in acute MS lesions. In some patients with MS, a supratentorial presentation can be associated with a tumefactive lesion.[71] Primary CNS neoplasms, metastases, or CNS infections are important considerations, particularly in the setting of a solitary lesion or evidence of diffuse or predominant cortical involvement. MRI characteristics including open ring or incomplete rim contrast enhancement, T2 hypointense rim, absent or mild mass effect, and absent or mild perilesional edema can help differentiate tumefactive demyelinating lesions from a primary CNS neoplasm.[72]In addition, a peripheral T2-hypointense rim, persistent T1-hypointensity, diffusion restriction with ADC correlate (particularly in an arc or ring pattern), and ring enhancement may point toward MS instead of a tumefactive demyelinating lesion associated with MOGAD.[73]

Neurological disorder progressing over twelve months or longer

Clinical considerations

Approximately 85% of patients with MS initially present with a CIS and a subsequent relapsing-remitting (RRMS) course.[21] However, sometimes MS is a consideration in patients with progressive neurologic syndromes. Such patients may have primary progressive MS (PPMS), or secondary progressive MS (SPMS) [74] with a previous relapsing course that was not recognized. MS-related progression usually manifests as asymmetric myelopathy, or, less commonly, as predominant ataxia or cognitive impairment, alone or incombination.[75] Clinical fluctuations in MS can make progression difficult to confirm, and longitudinal assessment of twelve months or greater is required by MS diagnostic criteria.[1] **Figure 4** highlights typical and atypical features of MS-associated progression.

In approaching the differential diagnosis in a patient presenting with suspected MS-associated progression, clinical history or evidence of previous attacks typical of MS (e.g. ON or short segment

myelitis) can point toward MS, as progressive neurological deficits rarely occur in other CNS inflammatory disorders that often mimic RRMS, such as AQ4-IgG+NMOSD and MOGAD.[76,77] Rapid progression of disability should prompt a broad evaluation for diagnoses other than MS, although a systemic non-neurological stressor (e.g. urinary tract infection) can temporarily worsen pre-existing deficits (i.e. a "pseudo-relapse") in patients with MS.[78] The multifocal pathology associated with MS typically leads to concurrent symptoms or neurological findings implicating more than one region of the CNS – an important finding pointing toward MS in patients with progressive presentations. Persistently monofocal or isolated symmetric progressive myelopathy or cerebellar ataxia should prompt a consideration of diagnoses other than MS (**Table 1**). While the phenotype of MS-related cognitive impairment can vary, its onset is usually insidious with impairments often, though not always, remaining mild to moderate and typically similar in severity to motor, sensory or other deficits. Severe or rapid isolated progressive cognitive impairment is atypical for MS, and should also prompt consideration of alternative disorders (**Table 1**). Neurological findings outside the CNS (e.g. peripheral neuropathy) and non-neurological symptoms and exam findings in the setting of progressive neurological deficits (e.g. arthritis, skin changes, cardiomyopathy, and gastrointestinal involvement) may also point toward specific diagnoses other than MS (**Table 1**).

Paraclinical considerations

MRI findings (**Table 2**) often aid the diagnosis of patients with progressive neurological deficits mimicking MS. Progressive myelopathy in the setting of T2-hyperintense spinal cord lesions that are longitudinally extensive, transverse (spanning the entire spinal cord), or central, should prompt a broad consideration of diagnoses other than MS. Absence of T2-hyperintense MRI spinal cord lesions in patients with progressive myelopathy is exceptionally atypical for MS, and suggests stiff person syndrome, HIV, amyotrophic or primary lateral sclerosis, hereditary spastic paraparesis, adrenomyeloneuropathy or functional neurological disorder. Progressive myelopathy accompanied by

MRI lesions that continue to expand or demonstrate persistent contrast enhancement over two months or longer could indicate inflammatory disorders such as neurosarcoidosis, neoplasm, or vascular malformations (e.g. dural arteriovenous fistula). In patients presenting with progressive ataxia, predominant or infiltrating brainstem and cerebellar lesions, large bilateral cerebellar peduncle lesions, or regional brainstem or cerebellar atrophy disorders other than MS should be considered (**Table 2**).[12] Diffuse symmetric T2-hyperintensities sparing the U-fibers in patients presenting with progressive and marked cognitive impairment should prompt consideration of HIV, leukodystrophies such as metachromatic leukodystrophy and X-linked adrenoleukodystrophy, and mitochondrial disorders.[79-81]

Blood and Cerebrospinal Fluid Laboratory Evaluation

There have been few attempts to develop or validate guidelines for CSF[82,83] or blood testing[84] in patients presenting with suspected MS. In clinical practice, a broad panel of blood testing is often obtained but typically is low yield,[23] as many contemporary disorders frequently referred for MS evaluation[3,4] are clinical diagnoses that would not be further clarified by such testing (e.g. migraine, small vessel ischemic disease, or functional neurological disorder). By contrast, AQP4-IgG, when tested in blood by cell-based assay, has high specificity for NMOSD.[85] While the diagnosis of MOGAD[14] requires the detection of MOG-IgG, low titres (i.e. ranging from 1:10 to less than 1:100) warrant caution and necessitate a higher threshold of clinical and MRI findings for diagnosis.[14,86] Testing for MOG-IgG close to a clinical event may increase the likelihood of detection of higher titres.[87] As possible, testing for AQP4-IgG or MOG-IgG before the initiation of immunomodulatory or immunosuppressive therapy is recommended to improve sensitivity. Numerous studies have reported increased prevalence of low titer systemic antibodies in patients with a confirmed diagnosis of MS and without concurrent antibody-mediated or systemic autoimmune disease (e.g. antinuclear antibodies, antiphospholipid antibodies, thyroid antibodies,

GAD).[88-90] Thus, focused blood testing guided by specific clinical or paraclinical findings (**Table 1** and **Table 2**) is preferable to a broad non-directed screening approach that carries the risk of false positive results and consequent additional unnecessary testing, misdiagnosis and inappropriate treatment.[22,23]

Figures 1-4 detail typical and atypical results of routine CSF testing in MS that aid differential diagnosis consideration. In MS, CSF is typically demonstrates a white cell count between 0 and 50 cells/µL with lymphocytic predominance. CSF protein level in MS is normal or mildly elevated. CSF pleocytosis of 50 cells/µL and above, or protein level greater than 100 mg/dL should result in a broad consideration of alternative inflammatory or infectious disorders. CSF-restricted oligoclonal bands (OCBs) are detected by isoelectric focusing combined with immunoblotting in approximately 85% of patients with MS[91] but occur in many conditions. OCBs can be absent early in MS, and appear on subsequent repeat testing.[92] OCBs are considerably less frequent in AQP4-IgG+NMOSD[93] and MOGAD (approximately 15%), [94] and the finding of negative CSF-restricted OCBs in patients with ON or myelitis should prompt consideration of these diagnoses and other disorders. In patients presenting with progressive neurological disability, normal CSF does not preclude MS but would be unusual and should direct evaluation toward metabolic, neurodegenerative, or structural disorders.

Differential Diagnosis Considerations in Specific Patient Populations

Age, race, ethnicity, and geographic region are important considerations in MS differential diagnosis. In children, it is important to exclude relapsing MOGAD (especially in patients age less than 11 years, given the rarity of MS in this age group and the relatively frequent detection of high titre serum MOG-IgG in young children with incident CNS demyelination).[95] Inherited or acquired genetic disorders with multifocal white matter lesions also must be considered, as many such disorders first manifest during childhood.[79,80] In older adults (i.e. >50 years), vigilance for atypical clinical or radiographic features of MS

and suggestive of specific disorders that increase in prevalence with age (e.g. MRI small vessel ischemic disease, spondylotic compressive myelopathy, and neoplasms) is necessary (**Table 1**).[43,95]

Recent data concerning the prevalence of MS from California in the United States, Manitoba Canada, and Northern Norway suggest that race, ethnicity, and genetic ancestry can influence potential risk of MS and these often complex demographic factors should also enter differential diagnosis considerations.[96-98] Furthermore, some racial and ethnic groups appear at increased risk for specific disorders that can mimic MS (e.g. higher prevalence of AQP4-IgG+NMOSD in East Asian and global Black populations compared to White populations, and higher prevalence of neurosarcoidosis in African American compared to White individuals in the US).[99,100] In addition, conflicting data in patients with MS have suggested possible differences in the prevalence of CSF OCBs according to ethnicity.[101-103] The prevalence of specific disorders known to mimic MS also varies by geographic region and differential diagnosis must consider, for instance, infectious,[104] inflammatory,[34] or nutritional disorders[105] that may be of higher prevalence in the specific region where the patient resides or has traveled. However, many of the disorders that commonly prompt evaluation for suspected MS (e.g. migraine, psychiatric disease, and MRI small vessel ischemic disease) do not differ in prevalence geographically.[3,4] Detailed consideration of the influence of age, race, ethnicity, genetic ancestry and region on approaches to MS differential diagnosis will be the topic of upcoming manuscripts resulting from this collaborative effort.

Differential Diagnosis Considerations and the Expanding Clinical and Radiological Spectrum of MS

Recent studies suggest the occurrence of an "MS prodrome"[18] – symptoms that are often non-specific but common in MS, such as fatigue, mood disorders, headache, sleep disturbances, and gastrointestinal disorders, and precede presentation with diagnostically specific neurological symptoms or signs of MS. Studies that have included cognitive, laboratory, or MRI evaluation [19,106,107] indicate that the disease

process likely begins years before a typical CIS and MS diagnosis. While prodromal symptoms can occur with early CNS damage associated with MS, in the absence of symptoms or exam findings adequate for MS diagnosis,[1] data concerning prodromal symptoms remain insufficiently specific to facilitate accurate differentiation of MS from other disorders.

Patients presenting with brain MRI lesions typical of MS fulfilling MRI criteria for dissemination in space but without a clinical presentation consistent with a typical CIS or neurological progression sufficient for MS diagnosis - termed radiologically isolated syndrome (RIS) – present a similar diagnostic challenge.[108,109] Differential diagnosis formulation should include the common diagnoses frequently mistaken for MS (i.e. migraine and MRI small vessel ischemic disease) that can sometimes fulfill MS MRI dissemination in space criteria.[110] Approximately half of patients diagnosed with RIS develop symptoms satisfying MS diagnostic criteria over a ten year follow-up period.[19] Spinal cord MRI and CSF examination can aid differential diagnosis of RIS and help stratify risk of MS.[19] However, detection of spinal cord lesions and OCBs in a patient with RIS does not preclude diagnoses other than MS, and a broad differential diagnosis is warranted. In many patients with RIS, diagnosis remains tentative and further clinical and radiographic monitoring over time is prudent.

Patients with prodromal MS or RIS lack sufficient typical symptoms or neurological exam findings for MS diagnosis. By contrast, patients with a syndrome recently termed “progressive solitary sclerosis” [20] present with symptoms and paraclinical findings typical of a progressive myelopathy associated with MS, yet also do not fulfill contemporary diagnostic criteria for MS. In this syndrome, insidious motor progression appears attributable to a single presumed demyelinating lesion typically located in the lateral columns or at the cervicomedullary junction,[20] but without clinical or MRI evidence of dissemination in space criteria.[1] While such patients appear to be within the clinical and radiographic spectrum of MS, careful exclusion of alternative diagnoses (e.g. alternative inflammatory or neoplastic

disorders) is necessary in such cases, and further data from larger cohorts is necessary to clarify differential diagnostic considerations.

Conclusions and future directions

Although knowledge relating to MS differential diagnosis has increased over the last decade, accurate diagnosis of MS continues to rely upon clinical acumen. Differential diagnosis formulation for MS requires a circumspect approach dependent upon the clinical presentation and accompanied by vigilance for clinical and paraclinical "red flags" suggesting alternative diagnoses. While the availability of AQP4-IgG and MOG-IgG tests have improved the ability to diagnose NMOSD and MOGAD and differentiate them from MS, comparable diagnostic biomarkers for MS remain a major unmet need[111] and the focus of recent ongoing research. For instance, CSF kappa free light chains have demonstrated comparable sensitivity and specificity for MS as OCBs,[112,113] and testing for kappa free light chains may prove more accessible than optimal OCBs assessment in some regions. Novel MRI findings, e.g. central vein sign and paramagnetic rim lesions,[114,115] have demonstrated potential to improve rapid diagnosis in patients with typical MS presentations and accurate diagnosis in patients with atypical or diagnostically challenging clinical or radiographic presentations. Emerging automated imaging techniques [116,117]incorporating these novel imaging findings have shown promise for differentiating lesions caused by MS from other disorders and may aid implementation of advanced imaging in routine clinical practice. In coming years, data from large prospective multicenter cohorts of patients undergoing evaluation for suspected MS [118] will be necessary to confirm the promise of putative MS biomarkers to complement clinical approaches aimed to ensure that there is "no better explanation" other than MS.

Search strategy and selection criteria

A research librarian performed a literature search in Ovid Medline from 1/1/2008 to 12/31/2022 using keywords “multiple sclerosis”, “diagnostic error”, “missed diagnosis”, “misdiagnosis”, “diagnostic accuracy”, and “differential diagnosis”, yielding 1430 unique citations. Covidence systematic review management software (Veritas Health Innovation, Melbourne, Australia) was utilized to review each abstract for relevance to the aims of the project. Four hundred seventy-six papers were retained, individually reviewed by AJS, and made available to all authors during manuscript development. Where possible, non-English language abstracts and manuscripts were translated to English by Google Translate and included. Additional relevant literature published after 1/1/2008 was also identified from the authors’ files during manuscript development.

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Figure Legend

Figure 1 title: Approach to MS differential diagnosis for patients presenting with suspected optic neuritis

Figure 2 title: Approach to MS differential diagnosis for patients presenting with suspected inflammatory brainstem or cerebellar syndrome

Figure 3 title: Approach to MS differential diagnosis for patients presenting with suspected myelitis

Figure 4 title: Approach to MS differential diagnosis for patients presenting with a progressive neurological disorder of twelve months or greater

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