The diagnosis and differential diagnosis of multiple sclerosis: progress and challenges

Dr Wallace J. Brownlee¹ FRACP
Dr Todd A. Hardy²,³ PhD
Prof Franz Fazekas⁴ MD
Prof David H. Miller¹,⁵ FMedSci

¹ Queen Square Multiple Sclerosis Centre, UCL Institute of Neurology, London, United Kingdom
² Neuroimmunology Clinic, Concord Hospital, University of Sydney, NSW, Australia
³ Brain & Mind Centre, University of Sydney, NSW, Australia
⁴ Department of Neurology, Medical University of Graz, Graz, Austria
⁵ NIHR University College London Hospitals Biomedical Research Centre, London, United Kingdom

Corresponding author: Dr Wallace Brownlee, Box 112, National Hospital for Neurology and Neurosurgery, Telephone +44 20 3108 7409, Fax +44 20 3448 3125, Email w.brownlee@ucl.ac.uk

Word count = 4268
Summary

The diagnosis of multiple sclerosis (MS) is based on typical neurological symptoms and signs along with evidence of dissemination of central nervous system (CNS) lesions in space and time. Magnetic resonance imaging (MRI) is often sufficient to confirm the diagnosis when characteristic lesions of MS accompany a typical clinical syndrome, but in some patients, further supportive information can be obtained from cerebrospinal fluid examination and neurophysiological testing. It is important to differentiate MS not only from other diseases in which demyelination is a feature e.g. neuromyelitis spectrum disorder (NMOSD) and acute disseminated encephalomyelitis (ADEM), but also non-demyelinating conditions such as chronic small vessel disease and other inflammatory, granulomatous, infective, metabolic and genetic causes that can mimic MS. Advances in MRI, serological and genetic tests have greatly helped in distinguishing MS from these conditions, but misdiagnosis can occur. In this review, we explore the progress and challenges in the diagnosis of MS with reference to diagnostic criteria, important differential diagnoses, current controversies and uncertainties, and future prospects.
Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated demyelinating disorder of the central nervous system (CNS). MS can present with alterations in sensation, mobility, balance, sphincter function, vision and cognition. Although the course is highly variable, many people develop irreversible disability, and MS remains a leading cause of neurological disability in young adults.

MS is classified based on the initial disease course as either relapsing-remitting (RRMS) or primary progressive (PPMS). RRMS is more common affecting 85-90% of patients and is characterised by relapses (episodes of neurologic dysfunction lasting at least 24 hours in the absence of fever or infection) followed by periods of remission. Recovery from relapses is variable and may be incomplete. RRMS typically affects young adults (mean age at onset 30 years) and women are affected three times as commonly as men. There is evidence that the incidence of RRMS may be increasing, particularly in women. PPMS (10-15% of patients) is characterised by an insidious, slowly progressive increase in neurological disability over time, usually without relapses. PPMS typically presents at an older age than RRMS (mean age at onset 40 years) and there is no gender bias. People with RRMS may develop a progressive course with time (secondary progressive MS) with a gradual increase in disability with or without relapses.

An early and accurate diagnosis of MS is essential because there are now effective treatments for RRMS. Currently, the diagnosis is based on clinical symptoms and signs and magnetic resonance imaging (MRI), which is highly sensitive to the detection of characteristic CNS lesions. Advances in MRI, immunological and genetic tests have improved the diagnosis of other conditions that can be mistaken for MS. A major discovery was the association between neuromyelitis optica spectrum disorder (NMOSD) and serum
aquaporin-4 IgG (AQP4-IgG), confirming that NMOSD is a different disease from MS requiring distinct treatments.\textsuperscript{4}

In this review, we discuss the diagnosis of MS including the approach to investigating patients with suspected MS, the diagnostic criteria for MS and their application in clinical practice. We cover key MS differential diagnoses with particular focus on other idiopathic inflammatory disorders including acute disseminated encephalomyelitis (ADEM) and NMOSD. Finally, we consider areas of controversy and uncertainty and the potential for future changes in diagnostic criteria.

**Diagnosis of MS**

*Presenting symptoms of MS*

The initial presentation of MS is varied and depends both on the location of lesions within the CNS and their onset (relapsing or progressive). Patients can present to a variety of doctors depending on the nature of their symptoms (e.g. GPs, ophthalmologists, orthopaedic surgeons) and if MS is suspected prompt referral to a neurologist is indicated.

Some common presenting symptoms and signs of MS and those either less common or suggestive of an alternative diagnosis are shown in Table 1. A first episode of neurologic dysfunction, presumably due to RRMS, is called a clinically isolated syndrome (CIS).\textsuperscript{2,5} Common CIS presentations include acute unilateral optic neuritis, a partial myelitis or a brainstem syndrome.\textsuperscript{5} Clinical features that suggest demyelination as the cause of such an episode include age <40 years, an acute/subacute onset over hours to days, maximal deficit within 4 weeks of onset and spontaneous remission. The onset of PPMS in contrast is characterised by slowly progressive symptoms, most often an asymmetric paraparesis that
evolves over months or years\(^6\) or, less commonly, a progressive hemiparesis or cerebellar ataxia or very rarely, visual failure or dementia.\(^6\)

In assessing a patient with suspected MS it is important to determine the onset and evolution of their symptoms and to seek details of previous neurological symptoms that could indicate an earlier unrecognised attack that may help establish the diagnosis and disease course (relapse or progressive onset). The neurological examination is important to localise the site of involvement in the CNS and may provide evidence of other lesions, for example pathologically brisk reflexes or an extensor plantar response in a patient with optic neuritis.

**Approach to investigating patients with suspected MS**

When a patient presents with symptoms or signs that could indicate MS, an MRI is essential as an abnormal brain MRI is seen in virtually all patients with established MS\(^7\) and over 80% of CIS patients who develop MS.\(^8\) MRI is also helpful in excluding other pathologies, for example, a compressive lesion in a patient with a progressive myelopathy, or identifying abnormalities that suggest an alternative diagnosis (e.g. leptomeningeal enhancement, longitudinally-extensive spinal cord lesion).

Brain MRI in MS typically shows multifocal T2-hyperintense white matter lesions (Figure 1) in characteristic locations: periventricular (including the corpus callosum), juxtacortical (abutting the cerebral cortex) and infratentorial regions.\(^9\) On T1-weighted images, lesions may appear hypointense (T1 “black holes”). Spinal cord lesions occur in 80-90% of patients with established MS and up to half of patients with CIS, most often in the cervical cord.\(^10,11\) Lesions extend over <1-2 vertebral segments and are often eccentrically placed abutting the
pial surface. Brain and spinal cord lesions may show enhancement after the administration of gadolinium (Figure 1).

A standardised MRI protocol was recently proposed by the MAGNIMS network to assist in the diagnosis of MS. In addition to obtaining brain images with an axial orientation, a sagittal T2 fluid-attenuated inversion recovery (FLAIR) sequence is recommended for detecting juxtacortical and corpus callosum lesions, which can be helpful in differentiating MS from other disorders. A post-contrast T1-weighted scan is recommended in patients with brain MRI lesions, to assist in diagnosis and differential diagnosis. Spinal cord MRI is recommended in patients with myelopathy or when MRI brain findings are not diagnostic of MS.

In most patients with a typical clinical picture and MRI findings a Cerebrospinal fluid (CSF) examination is usually not necessary, but can provide supportive evidence of MS. CSF findings in MS include a normal or mildly raised white cell count (<25 cells/cm³, predominantly lymphocytes) and protein (usually <1g/L), a raised IgG index and IgG oligoclonal bands (OCBs) not present in serum. Qualitative assessment of IgG using isoelectric focusing and immunofixation is the optimal method for detection of OCBs. OCBs are found in up to 90% of people with MS (less often in CIS patients) and sometimes in other neuroinflammatory disorders and their presence needs to be interpreted carefully. Neurophysiological testing of evoked potentials in visual, sensory or auditory pathways can also provide supportive evidence of MS by identifying a clinically silent lesion in the CNS indicating dissemination in space. A prolonged latency and well-preserved waveform on evoked potential testing is suggestive of demyelination but is not specific.
Laboratory investigations are often requested as part of the diagnostic work-up for MS. Routine testing for systemic autoimmune diseases has a very low-yield in patients with presentations typical of MS.\textsuperscript{17} Non-specific antibodies are frequently detected that may not be clinically relevant with low-titre antinuclear antibodies (ANA) particularly prevalent in patients with MS.\textsuperscript{17} Further targeted laboratory tests to exclude MS mimics might be indicated if the history, examination, or MRI findings are atypical.

\textit{Diagnostic criteria for MS and their application in clinical settings}

The diagnosis of MS requires objective evidence of CNS lesions disseminated in time and space. Historically, this has been on the basis of clinical findings alone requiring two separate attacks with signs of two or more lesions.\textsuperscript{18} The current diagnostic criteria for MS, the McDonald 2010 criteria, are shown in Panel 1. Using the McDonald 2010 criteria a diagnosis of MS can still be made on clinical grounds alone; however, MRI is used to provide evidence for dissemination in time and space, including in patients with CIS.\textsuperscript{1} For RRMS, MRI evidence of dissemination in space requires $\geq 1$ T2 lesion in at least two of four sites – periventricular, juxtacortical, and infratentorial regions and the spinal cord (Figure 1), with symptomatic lesions in the brainstem and spinal cord excluded.\textsuperscript{1} Dissemination in time requires either asymptomatic gadolinium-enhancing and non-enhancing lesions on the same MRI scan or a new lesion on a follow up scan.\textsuperscript{1} Using the McDonald 2010 criteria a diagnosis of RRMS can be made in up to one third of CIS patients with a single MRI scan.\textsuperscript{19}

The McDonald criteria provide separate recommendations for the diagnosis of PPMS which include CSF abnormalities in addition to MRI.\textsuperscript{1} Brain T2 lesion load tends to be lower in PPMS\textsuperscript{6} and the combination of MRI and CSF findings provides a higher sensitivity than MRI alone.\textsuperscript{20} Dissemination in space in suspected PPMS requires two or more of the following: (1) $\geq 1$ T2 brain lesion in at least one of the three sites typically affected in MS.
(periventricular, juxtacortical, infratentorial); (2) ≥2 T2 spinal cord lesions; (3) positive CSF (≥2 OCBs not present in serum, raised IgG index, or both). Progressive worsening over a period of at least 12 months provides evidence of dissemination in time.

The McDonald 2010 criteria are easily applied in a clinical setting and allow for an earlier diagnosis of MS.\textsuperscript{19} However, there are important caveats when using MRI criteria to diagnose MS. Firstly, the criteria are intended for use in patients in whom a diagnosis of MS is clinically suspected, rather than to differentiate MS from other neurological disorders. MRI in patients with small-vessel cerebrovascular disease, other inflammatory and non-inflammatory disorders affecting white matter (see examples in Tables 2 & 3), and even in healthy subjects (especially in older age groups), may show brain lesions that fulfil MRI criteria for MS\textsuperscript{21-24} The McDonald MRI criteria were developed and tested in CIS patients with symptoms typical of MS (e.g. unilateral optic neuritis) and they should not be applied to patients with non-specific neurological symptoms such as paraesthesia, dizziness or headache, in which the diagnosis is much less likely.\textsuperscript{23} Secondly, MRI criteria were tested and validated in European populations with a high incidence of MS\textsuperscript{25}, although recent studies investigating the McDonald 2010 criteria in CIS cohorts in Latin America\textsuperscript{26} and Asia\textsuperscript{27} have reported a similarly good performance. Finally the diagnosis of MS should only be made by a neurologist taking into account the clinical picture, MRI findings and the results of any other investigations.

\textit{The radiologically isolated syndrome}

The widespread use of MRI means incidental findings suggestive of MS are sometimes identified in some people who have no clinical symptoms. This is referred to as a radiologically isolated syndrome (RIS).\textsuperscript{28} The typical demyelinating lesions that characterise
RIS need to be carefully differentiated from small-vessel cerebrovascular disease and non-specific white matter lesions (the latter being common in people with migraine\textsuperscript{21,24}).

A third of RIS patients will develop clinical symptoms in the first 5 years of follow up (either a relapse or progressive symptoms).\textsuperscript{29} Younger age, male gender and gadolinium-enhancing, cortical or spinal cord lesions may be associated with an increased risk of developing MS.\textsuperscript{29-31} There are no accepted diagnostic criteria for RIS, but the Okuda 2009 criteria\textsuperscript{28} have been used in research studies and can also be applied in a clinical setting. These criteria consider only dissemination in space and are more stringent than the McDonald criteria, taking into account lesion size and morphology as well as location to help differentiate asymptomatic demyelinating lesions from other white matter lesions.

At this time it is considered essential that a diagnosis of MS only be made in a patient who has symptoms suggestive of demyelination.\textsuperscript{2} However, patients with RIS are at significant risk for developing MS and should be counselled and offered follow up as appropriate.

**MS in special patient populations**

**MS in children**

Up to 5% of people with MS develop their first symptoms in childhood, almost always RRMS.\textsuperscript{32} In younger children (<12 years) MS may present differently from adolescents and adults; encephalopathy, multifocal neurological deficits (often with prominent brainstem/cerebellar involvement) and seizures are more common.\textsuperscript{32} MRI findings may include large, confluent T2-hyperintense lesions that show remarkable resolution on follow-up scans.\textsuperscript{33} The clinical features and MRI findings may be suggestive of ADEM (see below). Older children (≥12 years) usually present with clinical features and MRI findings similar to
adults with CIS. The performance of the McDonald 2010 criteria has been tested in children with CIS and the criteria have a similar sensitivity/specificity for the development of MS as in adult populations but should not be applied in the setting of encephalopathy (i.e. ADEM).

**MS in older adults**

People presenting with MS after the age of 50 years have typically been classified as having late-onset multiple sclerosis. In this age group males are over-represented and a progressive onset is more common. Establishing a diagnosis of MS can be more difficult in older adults because white matter lesions due to small-vessel cerebrovascular disease are frequently found on brain MRI. In this situation a stringent interpretation of brain MRI criteria for MS is mandatory and spinal cord MRI is helpful since spinal cord lesions do not occur with healthy aging. A CSF examination looking for OCBs can also be particularly helpful in older adults, as may visual evoked potentials. Studies investigating MRI criteria for a diagnosis of MS have typically excluded patients older than 50 years and the McDonald criteria have not been investigated in this group.

**Atypical demyelinating lesions**

Brain lesions in MS are typically small (<1cm diameter) and ovoid with a homogenous signal on T2-weighted sequences. Occasionally, MS presents with an atypical demyelinating lesion characterised by their large size (>2cm diameter, sometimes with peri-lesional oedema and mass effect), enhancement pattern (open or closed-ring enhancement) or morphology (infiltrative or heterogeneous appearance including concentric rings). These lesions may have the appearance of a neoplasm (glioma, primary CNS lymphoma) or infection (brain abscess, progressive multifocal leukoencephalopathy), sometimes necessitating brain biopsy. While some patients presenting with atypical demyelinating
lesions have a monophasic course, 30-60% develop MS. MRI might help predict outcome; the presence of typical MS lesions and a closed-ring enhancement pattern have been associated with a higher risk of MS. Atypical demyelinating lesions are also seen in NMOSD and ADEM.

Differential diagnosis of MS

The differential diagnosis of MS is broad and many neurologists use the approach of identifying “red flag” clinical, imaging or other laboratory features that suggest an alternative diagnosis. The differential diagnosis depends on the clinical presentation with different considerations in patients with relapsing or progressive courses. These disorders include several closely related idiopathic inflammatory CNS diseases, along with a range of other disorders that may involve white matter including inherited leukodystrophies, vasculopathies, metabolic disorders and other neuroinflammatory diseases (e.g. sarcoidosis, vasculitis, Behcet’s disease). Although a comprehensive differential diagnosis is beyond this review, Tables 2 and 3 provide further information on a limited number of disorders that, in our experience, can be confused with MS. Selected idiopathic inflammatory disorders in which demyelination is a feature are discussed in more detail below.

Acute disseminated encephalomyelitis (ADEM)

ADEM is an inflammatory demyelinating disorder of the CNS distinct from MS that occurs mainly in childhood and is rare in adults. Patients present with multifocal neurological deficits and encephalopathy sometimes with a history of antecedent infection or vaccination. MRI findings include large (>1-2cm), bilateral white matter lesions and deep grey matter lesions and contrast enhancement. CSF findings include a lymphocytic pleocytosis and raised protein. CSF OCBs may only be present transiently. The clinical, imaging and laboratory features of ADEM and MS overlap and diagnostic criteria emphasise the requirement of
encephalopathy (altered level of consciousness, behavioural or cognitive change) in making the diagnosis of ADEM (Supplementary Panel 1). ADEM is almost always monophasic; however, an encephalopathic ADEM-like illness can sometimes be the first presentation of MS in both children and adults and diagnostic criteria for ADEM remain imperfect.

Neuromyelitis optica spectrum disorder (NMOSD)

NMOSD is an inflammatory astrocytopathy of the CNS with clinical and radiological features that overlap with MS. The identification of a pathogenic IgG antibody directed against the aquaporin-4 (AQP4-IgG) water channel has established NMOSD as a specific disease entity that needs to be differentiated from MS because of important differences in prognosis and treatment. NMOSD is approximately 100 times less common than MS in European and North American populations but is relatively more common in Asia and Africa where MS is less common. NMOSD shows a strong gender bias (female: male ratio up to 9:1) and a mean age at onset of 39 years, although all age groups can be affected including children and the elderly. A history of autoimmunity including thyroid disease and connective tissue disorders (e.g. systemic lupus erythematosus, Sjogren’s syndrome) is not uncommon. Most patients with NMOSD have a relapsing course with accumulation of disability over time related to poor recovery from individual attacks and a secondary progressive course is rare. An accurate diagnosis of NMOSD is essential since prompt treatment of acute attacks and long-term immunosuppression appear to reduce disability, while conventional MS treatments may aggravate NMOSD.

The core clinical features of NMOSD are optic neuritis and transverse myelitis. Compared with MS, optic neuritis in NMOSD is more likely to be bilateral (either simultaneous or rapidly sequential) and associated with poor visual recovery. Lesions extending over more than half the length of the optic nerve, and sometimes into the optic chiasm are characteristic of
Attacks of myelitis are associated with longitudinally-extensive spinal cord lesions on MRI (≥3 vertebral bodies) with prominent involvement of the central cord (Supplementary Figure 4), in contrast to MS where lesions are usually short (<1-2 vertebral bodies) and located peripherally. Brain involvement also occurs in NMOSD especially in areas rich in aquaporin-4 such as the dorsal medulla/area postrema (where lesions may cause intractable nausea, vomiting and hiccoughs), diencephalon, and periependymal regions of the corpus callosum, third and fourth ventricles (Supplementary Figure 1). Recently it has been recognised that some patients with NMOSD have brain lesions that may be difficult to distinguish from MS, with up to a quarter fulfilling Barkhof criteria. CSF occasionally shows features distinct from MS (white cell count >50 cells/cm³, neutrophils or eosinophils >5 cells/cm³); however, a mild CSF pleocytosis is more common (white cell count <25 cells/cm³). In contrast to MS CSF OCBs are uncommon in patients with NMOSD (<20%).

Approximately 70% of patients with relapsing NMOSD are AQP4-IgG positive, with the sensitivity increased with the use of cell-based rather than ELISA assays. AQP4-IgG is highly specific for NMOSD, although false positives occur in up to 0.5% of MS patients using ELISA assays, potentially resulting in misdiagnosis. A recently identified subgroup of AQP4-IgG seronegative NMOSD patients have antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) and may have a more favourable course. MOG-IgG is also found in some patients with ADEM (particularly in children), and in ADEM followed by optic neuritis, and isolated or recurrent optic neuritis. It is not clear whether MOG-IgG-associated inflammatory demyelinating syndromes will remain part of NMOSD or be considered as a distinct nosologic entity in the future.
Diagnostic criteria for NMOSD have recently been updated (Supplementary Panel 2).\textsuperscript{47} The diagnostic criteria are more stringent in AQP4-IgG negative patients requiring at least two attacks affecting different sites, one of which must be optic neuritis, myelitis or an area postrema syndrome.

Although the first attack of NMOSD can mimic CIS (e.g. acute unilateral optic neuritis or short-segment partial myelitis\textsuperscript{61}), routine testing for AQP4-IgG in CIS populations with a high incidence of MS and low incidence of NMOSD has a very low yield and is not recommended.\textsuperscript{62} A first demyelinating event suggestive of NMOSD (e.g. severe or bilateral optic neuritis, longitudinally-extensive transverse myelitis, area postrema syndrome) should always mandate testing for AQP4-IgG and facilitates an earlier diagnosis and treatment.

**Misdiagnosis of multiple sclerosis**

Rates of misdiagnosis of MS may be as high as 10\%.\textsuperscript{63} In a survey of MS specialist neurologists in the United States, 95\% of respondents had seen one or more patients in the previous year who had been misdiagnosed with MS, many of whom were being treated inappropriately with disease-modifying therapies. The major disorders identified that were misdiagnosed as MS were small-vessel cerebrovascular disease, migraine, fibromyalgia and functional neurological disorders.\textsuperscript{64} These disorders usually present quite differently to MS and reasons for misdiagnosis included misinterpretation of clinical findings (symptoms not typical of demyelination, absence of objective neurological signs) and inappropriate application of MRI criteria.\textsuperscript{63} The application of McDonald criteria and the diagnosis of MS should be undertaken by neurologists who are familiar with MS with additional expert advice when needed (e.g. MRI review by a neuroradiologist).
Controversies and areas of uncertainty

Although there has been major progress in diagnosing MS, areas of uncertainty remain. The role of spinal cord imaging and CSF examination in MS diagnosis is particularly controversial. Current guidelines recommend spinal cord MRI in patients with symptoms of myelopathy or when brain MRI findings are not diagnostic of MS. However, spinal cord lesions can be very helpful in making a diagnosis of MS (cord lesions do not occur with healthy aging or cerebrovascular disease and provide additional evidence of dissemination in space) and may provide important prognostic information. Therefore routine imaging of the whole spinal cord in all patients with suspected MS has recently been proposed. The McDonald 2010 criteria do not mandate a CSF examination and there is much variation between neurologists as to how often a lumbar puncture is done in the diagnosis of MS. As noted previously the sensitivity of OCBs is <100% and may be significantly lower in people with a first demyelinating event, the time when a lumbar puncture is most likely to be performed. However, OCBs may provide additional prognostic information and may increase diagnostic confidence, especially when considering long-term disease-modifying treatment.

Gadolinium-enhancing lesions provide evidence for dissemination in time and can also assist in differential diagnosis. Current guidelines recommend a post-contrast T1-weighted scan as part of the diagnostic evaluation of patients with suspected MS. The United States Food and Drug Administration and the European Medicines Agency are investigating the clinical significance of gadolinium deposits in the brain reported in some patients after the repeated use of gadolinium-based contrast agents. At this time, the safety concern should not preclude the use of gadolinium-based contrast agents for diagnostic purposes but should be considered in monitoring patients with MS.
MRI criteria for MS require a balance between sensitivity (diagnosing MS at an early stage) and specificity (making an accurate diagnosis). The optimal balance of sensitivity and specificity using MRI criteria is uncertain. Using the McDonald criteria, MS is being diagnosed significantly earlier than with the use of clinical criteria alone facilitating earlier treatment. However, the criteria are intended to provide diagnostic rather than prognostic information. Conventional brain MRI findings around the time of diagnosis are only modestly predictive of long-term disability and there is uncertainty as to the extent to which criteria for diagnosis and treatment should be linked. The McDonald criteria identify a subgroup of patients with a single attack and MRI evidence of dissemination in time and space who do not experience further relapses even with long-term follow-up. In the past this group would be considered to have CIS rather than MS. The changes to the diagnostic criteria may be favourably shifting the apparent long-term outcome of MS (the so called "Will Rogers phenomenon"), independent of any effect of disease-modifying treatments.

Conclusions and future perspectives

Current diagnostic criteria for MS integrate clinical and MRI findings and enable an earlier and more reliable diagnosis of MS than with clinical findings alone, potentially facilitating earlier treatment. The criteria are best applied in an individual patient when there are typical symptoms and signs of MS and when relevant differential diagnoses have been excluded. Further supportive information from CSF and/or evoked potentials can be obtained if diagnostic uncertainty remains.

Despite the current usefulness of the McDonald criteria, the MAGNIMS network have recently proposed a number of modifications, such as inclusion of optic nerve, cortical and symptomatic lesions in dissemination in space and standardisation of dissemination in space criteria for RRMS, PPMS and RIS. Some of these recommendations are evidence-
based\textsuperscript{73,74} and others are based on expert consensus. These and other changes to the diagnostic criteria for MS will be considered at a meeting of an international panel in late 2016.

Further iterations of the McDonald criteria may allow for inclusion of new and emerging MRI techniques with improved pathological specificity.\textsuperscript{12,68} Cortical grey matter is frequently involved in MS pathologically, but cortical lesions are rarely visualised on conventional MRI sequences and are better seen using double inversion recovery (DIR) or phase-sensitive inversion recovery (PSIR) techniques.\textsuperscript{73,75} Cortical grey matter lesions may be helpful in making a diagnosis of MS\textsuperscript{68,73} and have not been found in NMOSD\textsuperscript{76} or migraine.\textsuperscript{24} MS lesions characteristically have a perivenular distribution and using T2* or susceptibility-weighted imaging a central vein can be detected in most MS lesions, especially at higher field strengths.\textsuperscript{77} The presence of a “central vein sign” might help differentiate MS from NMOSD\textsuperscript{78} and white matter lesions due to small vessel disease, migraine, and healthy aging.\textsuperscript{77} Research is also focused on novel CSF and body fluid biomarkers that are associated with the development of MS in patients with CIS including CSF IgM-OCBs, MRZ-specific IgG, kappa free light chains, CXCL13, chitinase-3-like protein 1 and neurofilament light chain.\textsuperscript{79} However, their utility in differentiating MS from other disorders is yet to be established. Optical coherence tomography (OCT) is also being investigated as an MS biomarker. Evidence that retinal nerve fibre layer thinning occurs in MS means that OCT has potential utility as a predictor of progression from CIS to MS\textsuperscript{96} and OCT findings may assist in differentiating MS from NMOSD\textsuperscript{80} and Susac’s syndrome.\textsuperscript{81}

The diagnosis of MS and its many differential diagnoses can still be challenging but progress continues to be made. Diagnostic criteria for both MS and NMOSD have changed in recent years as new pathological, immunological, imaging, clinical and therapeutic findings have
emerged. It is likely that there will be future changes in diagnostic criteria for MS and other CNS inflammatory disorders as new knowledge and clinical experience evolves.
Table 1. Typical presentations of relapsing-remitting MS and selected atypical presentations that are more suggestive of an alternative diagnosis.

<table>
<thead>
<tr>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute unilateral optic neuritis</td>
<td>Bilateral optic neuritis, or unilateral optic neuritis with a poor visual recovery</td>
</tr>
<tr>
<td>Double vision due to an internuclear ophthalmoplegia or sixth nerve palsy *</td>
<td>Complete gaze palsy or fluctuating ophthalmoparesis</td>
</tr>
<tr>
<td>Facial sensory loss or trigeminal neuralgia *</td>
<td>Intractable nausea, vomiting or hiccups</td>
</tr>
<tr>
<td>Cerebellar ataxia and nystagmus</td>
<td>Complete transverse myelopathy with bilateral motor/sensory involvement</td>
</tr>
<tr>
<td>Partial myelopathy</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td>- Sensory symptoms</td>
<td>Subacute cognitive decline</td>
</tr>
<tr>
<td>- Lhermitte’s symptom</td>
<td>Headache, meningism</td>
</tr>
<tr>
<td>- Asymmetric limb weakness</td>
<td>Isolated fatigue / asthenia</td>
</tr>
<tr>
<td>- Urge incontinence, erectile dysfunction</td>
<td>Constitutional symptoms</td>
</tr>
</tbody>
</table>

* In a young adult (< 40 years)
Table 2. Differential diagnosis of multiple sclerosis: selected disorders with a relapsing-remitting course.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical features</th>
<th>MRI findings</th>
<th>CSF findings</th>
<th>Other investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMOSD</td>
<td>Optic neuritis – especially bilateral or with visual poor recovery Transverse myelitis Intractable nausea and vomiting Paroxysmal tonic spasms</td>
<td>Longitudinally-extensive optic nerve lesions (involving &gt;50% of the optic nerve) +/- extension into the optic chiasm Brain lesions in diencephalon, dorsal midbrain, periependymal regions; “cloudlike” enhancement Longitudinally-extensive spinal cord lesions extending over ≥3 vertebral segments</td>
<td>Mild CSF pleocytosis sometimes with neutrophils or eosinophils OCBs present 20%</td>
<td>AQP4-IgG MOG-IgG +/- OCT</td>
</tr>
<tr>
<td>Neurosarcoiosis</td>
<td>Optic neuropathy and myelopathy; facial palsy Early relapse after stopping steroids +/- Systemic involvement</td>
<td>Meningeal enhancement Enhancement of the optic nerve sheath Persistent, nodular enhancement within lesions Enlarged lacrimal glands</td>
<td>OCBs sometimes present Raised CSF ACE level (not sensitive or specific for neurosarcoiosis)</td>
<td>Serum ACE level Chest x-ray, HRCT, lung function tests CT/PET scan Slit-lamp examination Tissue biopsy</td>
</tr>
<tr>
<td>CNS vasculitis</td>
<td>Headache, acute CNS syndromes including hemiparesis and ataxia Early cognitive impairment +/- Systemic involvement</td>
<td>Punctate or larger lesions in the grey and white matter, often enhancing, sometimes with restricted diffusion and evidence of micro-haemorrhages</td>
<td>OCBs sometimes present</td>
<td>Serum ANCA (systemic vasculitis) Tissue biopsy – systemic site or brain biopsy (if possible)</td>
</tr>
<tr>
<td>Susac’s syndrome</td>
<td>Encephalopathy, visual loss, deafness</td>
<td>“Snow-ball” lesions in the corpus callosum associated with restricted diffusion in the acute phase and then T1-hypointensity; also “icicle” and “spoke” lesions</td>
<td>OCBs usually absent</td>
<td>Fluorescein angiogram looking for branch retinal artery occlusions OCT Audiogram</td>
</tr>
<tr>
<td>CADASIL</td>
<td>Migraine, especially with complex or prolonged aura Recurrent acute hemiparesis and other vascular syndromes Neuropsychiatric disturbance Dementia</td>
<td>Extensive white matter abnormalities; prominent involvement of the temporal poles and external capsule</td>
<td>OCBs absent</td>
<td>Testing for NOTCH3 gene mutation Skin biopsy</td>
</tr>
<tr>
<td>Connective tissue disorders (SLE, Sjogren’s syndrome, antiphospholipid syndrome)</td>
<td>Optic neuritis, longitudinally extensive transverse myelitis, Systemic involvement Recurrent miscarriage, thrombosis (antiphospholipid syndrome)</td>
<td>Variable</td>
<td>OCBs usually absent</td>
<td>Serologic testing – ANA, ENA, antiphospholipid antibodies AQP4-IgG</td>
</tr>
<tr>
<td>Behet’s disease</td>
<td>Brainstem syndrome, myelopathy (rare) Oral and genial ulceration Intraocular inflammation</td>
<td>Mass-like enhancing lesions, predilection for the midbrain, thalami and internal capsules</td>
<td>Significant pleocytosis (WCC &gt;50 cells/cm³), may be neutrophil predominant OCBs usually absent</td>
<td>Pathergy testing HLA typing</td>
</tr>
<tr>
<td>CLIPPERS</td>
<td>Subacute ataxia, double</td>
<td>Punctate gadolinium-</td>
<td>OCBs sometimes present</td>
<td>Brain biopsy</td>
</tr>
<tr>
<td>Condition</td>
<td>Symptoms</td>
<td>Imaging findings</td>
<td>OCBs Status</td>
<td>Genetic Testing</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Leber’s hereditary optic neuropathy</td>
<td>Bilateral sequential optic neuropathies with poor visual recovery</td>
<td>Normal or may show white matter lesions (Harding’s disease)</td>
<td>OCBs absent</td>
<td>Genetic testing</td>
</tr>
<tr>
<td></td>
<td>Males &gt; females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>enhancing lesions within the brainstem and cerebellum +/− lesions in the basal ganglia, supratentorial white matter and spinal cord</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Differential diagnosis of multiple sclerosis: selected disorders with a progressive course.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical features</th>
<th>MRI findings</th>
<th>CSF findings</th>
<th>Other investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTLV1-associated myelopathy</td>
<td>Progressive myelopathy Residence or travel to an endemic area (especially West Indies, Japan)</td>
<td>Spinal cord atrophy (thoracic &gt; cervical) T2-hyperintense brain lesions in some patients</td>
<td>OCBs sometimes present</td>
<td>CSF HTLV1 antibody testing</td>
</tr>
<tr>
<td>Dural AV fistula</td>
<td>Subacute, progressive myelopathy</td>
<td>Extensive spinal cord T2-hyperintensity often extending to the conus +/- gadolinium enhancement Dilated veins over the dorsal surface of the cord (often subtle) Brain MRI normal</td>
<td>OCBs absent</td>
<td>Spinal angiogram</td>
</tr>
<tr>
<td>Nutritional myelopathy (vitamin B12 or copper deficiency)</td>
<td>Subacute progressive myelopathy or myeloneuropathy Optic atrophy (severe B12 deficiency) Anaemia or pancytopenia</td>
<td>T2-hyperintensity upper cervical cord classically affecting the posterior columns Brain MRI normal</td>
<td>OCBs absent</td>
<td>Serum B12, methylmalonic acid Serum copper levels, caeruloplasmin</td>
</tr>
<tr>
<td>Primary lateral sclerosis (or upper motor neurone predominant ALS)</td>
<td>Spastic quadriplea or hemiparesis +/- Bulbar involvement +/- Development of lower motor neurone signs</td>
<td>MRI normal or showing T2-hyperintensity in the corticospinal tracts</td>
<td>OCBs absent</td>
<td>EMG looking for lower motor neurone involvement</td>
</tr>
<tr>
<td>Leukodystrophies - Adrenomyeloneuropathy - Krabbe's disease - Alexander's disease - Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS)</td>
<td>Progressive myelopathy (adrenomyeloneuropathy, Krabbe's) Bulbar symptoms, ataxia (Alexander's disease) Early cognitive impairment (HDLS)</td>
<td>Highly variable Diffuse, symmetrical T2-hyperintensity sparing subcortical U fibres; with posterior hemispheric predominance (adrenomyeloneuropathy) Spinal cord MRI normal or showing atrophy</td>
<td>OCBs absent</td>
<td>Very-long chain fatty acids (adrenomyeloneuropathy) Genetic testing available for some leukodystrophies</td>
</tr>
<tr>
<td>Hereditary spastic paraplegia (especially SPG5)</td>
<td>Slowly progressive myelopathy (spasticity&gt;weakness) +/- Other neurological symptoms +/- Family history</td>
<td>Spinal cord atrophy Supratentorial and infratentorial white matter lesions (SPG5) Atrophy of the corpus callosum</td>
<td>OCBs absent</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>Spinocerebellar ataxias</td>
<td>Progressive cerebellar ataxia +/- Other neurological symptoms +/- Family history</td>
<td>Early, prominent cerebellar +/- spinal cord atrophy</td>
<td>OCBs absent</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>Clinical scenario</td>
<td>Additional evidence required</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 attacks with objective evidence of</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 lesions</td>
<td>Dissemination in space demonstrated by:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 attacks with objective evidence of</td>
<td>- ≥1 T2 lesion in at least 2 of 4 areas of the CNS typically affected in demyelination: periventricular, juxtacortical, infratentorial, spinal cord (Figure 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 lesion</td>
<td>- Second clinical attack at a different site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 attack with objective evidence of</td>
<td>Dissemination in time demonstrated by:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 lesions</td>
<td>- Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions on a single scan or a new T2 and/or gadolinium-enhancing lesion on follow-up MRI (Figure 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 lesion</td>
<td>- Second clinical attack</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 attack with objective evidence of</td>
<td>Dissemination in space demonstrated by:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 lesion</td>
<td>- ≥1 T2 lesion in at least 2 of 4 areas of the CNS typically affected in demyelination: periventricular, juxtacortical, infratentorial, spinal cord</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One year of disease progression</td>
<td>Dissemination in time demonstrated by:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(retrospectively or prospectively</td>
<td>- Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions on a single scan or a new T2 and/or gadolinium-enhancing lesion on follow-up MRI (Figure 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>determined)</td>
<td>- Second clinical attack</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two of the following:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- ≥1 T2 brain lesions in at least one MS-characteristic regions (periventricular, juxtacortical, or infratentorial)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- ≥2 T2 spinal cord lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Positive CSF (≥2 oligoclonal bands not present in serum, elevated IgG index, or both)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Locations of typical multiple sclerosis lesions in the brain and spinal cord indicated by white arrows. Axial brain MRI scans showing multiple periventricular lesions (a) with contrast enhancement of one lesion (b), juxtacortical lesions (c) and infratentorial lesions (d). Sagittal (e,f) and axial (g,h) scans with a cervical spinal cord lesion showing contrast enhancement in (f,h)
Supplementary Panel 1. Diagnostic criteria for acute disseminated encephalomyelitis (modified from Krupp et al 2013\textsuperscript{32})

1. A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause
2. Encephalopathy that cannot be explained by fever
3. No new clinical and MRI findings emerge three months or more after the onset
4. Brain MRI is abnormal during the acute (three-month) phase. Typical brain MRI findings include:
   - Diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter
   - T1 hypointense lesions in the white matter are rare
   - Deep grey matter lesions (e.g. thalamus or basal ganglia) can be present
<table>
<thead>
<tr>
<th>Supplementary Panel 2. Neuromyelitis optica spectrum disorder (modified from Wingerchuk et al 2015&lt;sup&gt;4&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core clinical characteristics</strong></td>
</tr>
<tr>
<td>1. Optic neuritis</td>
</tr>
<tr>
<td>2. Acute myelitis</td>
</tr>
<tr>
<td>3. Area postrema syndrome (an episode of otherwise unexplained hiccups or nausea and vomiting)</td>
</tr>
<tr>
<td>4. Acute brainstem syndrome</td>
</tr>
<tr>
<td>5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions</td>
</tr>
<tr>
<td>6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions</td>
</tr>
<tr>
<td><strong>Diagnostic criteria for NMOSD with AQP4-IgG</strong></td>
</tr>
<tr>
<td>1. At least 1 core clinical characteristic</td>
</tr>
<tr>
<td>2. Positive test for AQP4-IgG using best available detection method</td>
</tr>
<tr>
<td>3. Exclusion of alternative diagnoses</td>
</tr>
<tr>
<td><strong>Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status</strong></td>
</tr>
<tr>
<td>1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:</td>
</tr>
<tr>
<td>a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome</td>
</tr>
<tr>
<td>b. Dissemination in space (2 or more different core clinical characteristics)</td>
</tr>
<tr>
<td>c. Fulfilment of additional MRI requirements, as applicable (see Wingerchuk et al 2015&lt;sup&gt;4&lt;/sup&gt;)</td>
</tr>
<tr>
<td>2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable</td>
</tr>
<tr>
<td>3. Exclusion of alternative diagnoses</td>
</tr>
</tbody>
</table>
Supplementary Figure 1. T2-weighted MRI scans in AQP4-IgG positive neuromyelitis optica spectrum disorder (NMOSD).
(A) a longitudinally extensive spinal cord lesion (arrows); (B) a lesion involving the central spinal cord (arrow heads); (C) a lesion in the dorsal medulla (arrow); (D) multifocal lesions around the lateral ventricles, third ventricle and diencephalon.
Search strategy and selection criteria

We searched MEDLINE (01 January 1995 – 15 May 2016) using the search terms “multiple sclerosis”, “neuromyelitis optica”, “acute disseminated encephalomyelitis”, “diagnosis”, “diagnostic criteria” and “differential diagnosis” for articles published in the English language. Additional articles were also sought from the reference lists of relevant articles. Priority was given to new studies published in the last 5 years. Where appropriate review articles have been referenced to provide more detailed information on individual topics.

Contributions

WJB performed the literature search. WJB and DHM planned the outline of the manuscript and drafted the text. All of the authors edited the manuscript, tables and figures. DHM accepts responsibility for the final manuscript.

Acknowledgements

Kate Brunskill, Deputy Librarian, Queen Square Library, Archive & Museum assisted in planning and conducting the literature search. The Queen Square Multiple Sclerosis Centre at UCL Institute of Neurology is supported by the United Kingdom MS Society and UCL-UCLH Biomedical Research Centre.

Declaration of interests

WJB has nothing to disclose.

TAH has received honoraria for talks and advisory boards, and support for scientific meetings from Novartis, Biogen Idec, Merck-Serono, Alexion and Genzyme.

FF serves on scientific advisory boards for Bayer-Schering, Biogen Idec, Genzyme, Merck Serono, Pfizer, Novartis, Parexel and Teva Pharmaceutical Industries Ltd and has received speaker honoraria and support from Biogen Idec, Bayer Schering, Merck Serono, Novartis, Pfizer, Sanofi-Aventis, Shire and Teva Pharmaceutical Industries Ltd.

DHM has received honoraria through payments to his employer, UCL Institute of Neurology, for Advisory Committee and/or Consultancy advice in MS studies from Biogen Idec, Novartis, Mitsubishi Pharma Europe and Bayer Schering Pharma; compensation through
payments to his employer for performing central MRI analysis of MS trials from Biogen Idec, Novartis and Apitope.

References


