The current role of MRI in differentiating multiple sclerosis from its imaging mimics

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Abstract

MRI red flags proposed over a decade ago by the European Magnetic Resonance Network in MS (MAGNIMS) have guided clinicians in the diagnosis of multiple sclerosis (MS). However, the past 10 years has seen increased recognition that vascular disease can coexist and possibly interact with MS, improvements in the reliability of ways to differentiate MS from novel antibody-mediated CNS disorders, such as anti-aquaporin-4 antibody and myelin oligodendrocyte glycoprotein antibody associated diseases, and advances in MRI techniques. In this Review, MAGNIMS updates the imaging features that differentiate the most common mimics of MS, particularly age-related cerebrovascular disease and neuromyelitis optica, from MS itself. We also provide a pragmatic summary of the clinically useful MRI features that distinguish MS from its mimics, and discuss the future of non-conventional techniques that have identified promising disease-specific features.

[H1] Introduction

The diagnosis of multiple sclerosis (MS) is usually straightforward in patients who present with a typical clinical history. When symptoms that are not specific to or are atypical for MS occur, however, ancillary tests have a more dominant role. MRI is the most commonly performed investigation that can support a clinical diagnosis of MS[1,2] and, for a considerable proportion of patients, can even replace some clinical criteria by revealing brain and spinal cord changes that are typical for MS. MRI can also be useful for ruling out alternative neurological diseases[3].

The diagnostic criteria for MS focus on white matter lesion (WML) abundance and dissemination in space and time[4], but these criteria alone cannot confirm a diagnosis of MS or rule out other diagnoses because WMLs occur in many diseases and clinical conditions. Therefore, characteristics such as lesions at different ages (acute and chronic), Dawson fingers, juxta-cortical lesions, and short partial and eccentric spinal cord lesions can support a diagnosis of MS[2,5,6] (**Figure 2)**. However, diagnostic imaging criteria[1,2,4,7] were created to predict the development of MS in patients with a clinically isolated syndrome (CIS) that suggests inflammatory demyelination, and therefore in the context of a clinical presentation typical of MS. If used outside of this context in an attempt to distinguish MS from other disorders, such criteria might not perform well because they are fulfilled by a considerable proportion of patients with other neurological diseases (**Table 1**)[8–16]. Their use in this way could, therefore, lead to unnecessary anxiety, misdiagnosis and inappropriate treatment[17].

Red flags that were described over a decade ago by the European Magnetic Resonance Network in MS (MAGNIMS)[18] have guided clinicians who are considering a diagnosis of MS, but several new developments in the MS imaging field have occurred in the past decade. First, the coexistence of age-related changes and vascular disease has been recognized in patients with MS, and these comorbidities pose particular diagnostic challenges. Second, features have been described that distinguish MS from the newly recognized antibody-mediated syndromes of neuromyelitis optica spectrum disorders (NMOSDs) and acute demyelinating encephalomyelitis (ADEM), associated with anti-aquaporin-4 (AQP4) antibodies and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies. Last, advances in the latest MRI techniques have identified promising disease-specific features.

Taking these developments into account, a MAGNIMS workshop was held for three purposes. First, to update the imaging features that differentiate between MS and its most common imaging mimics, particularly age-related cerebrovascular disease, NMOSD (including anti-MOG antibody associated disease) on 1.5–3T conventional MRI using clinical diagnostic sequences[19] (for example, T2-weighted and T2-weighted fluid-attenuated inversion recovery (T2-FLAIR), and pre-contrast and post-contrast weighted scans)[20]. 7T data was not considered in this review owing to the limited clinical relevance at present. Second, to determine the utility of other MRI techniques, such as susceptibility weighted imaging (SWI) double inversion recovery (DIR), proton MR spectroscopy (MRS), magnetization transfer ratio (MTR) and diffusion tension imaging (DTI), which appear promising in identifying disease-specific features [21]. Finally, we also examined advances that have been made in identifying imaging hallmarks that can differentiate relatively uncommon MS mimics from MS. In this Review, we present the findings of this workshop in relation to the use of MRI to distinguish MS from other white matter disorders, and propose a practical diagnostic algorithm (Fig. 1).

[H1] Cerebrovascular disease and ageing

[H2] Imaging similarities to MS

Most neurologists and neuroradiologists would be unsure of the diagnosis for a 50-year-old patient who smoked and presented with progressive walking difficulties and WMLs on brain MRI. This difficulty is because the most common cause of WMLs is age-related changes and/or vascular disease, but MS lesions can look similar[22–24]. WMLs can indicate diverse underlying processes related to a broad spectrum of vascular disorders, amongst which cerebral small vessel disease (SVD) is particularly important. SVD is pathologically heterogeneous and best considered as a group of diseases[25] rather than a single entity (**Table 2**). Small vessels, such as veins and arterioles with a diameter <500 μm, cannot be studied easily *in vivo*, and signs of parenchymal damage, such as WMLs, lacunae, widened Virchow–Robin spaces and microbleeds, are used as MRI surrogate markers for SVD[26] (**Fig. 3**). These vascular features become more numerous with age and influence functional outcomes and mortality[27,28].

Age-related white matter changes are heterogeneous[29]. Periventricular pencil-thin lining of the ventricles is commonly seen in normal ageing (frequently already detectable in the fifth to sixth decades of life), followed by so-called caps (hyperintense lining of the frontal and occipital horns of the lateral ventricle; **Fig. 3**) and bands (thicker hyperintense lining parallel and adjacent to the walls of the lateral ventricles), which can indicate ependymal loss, subependymal gliosis and widened extracellular spaces. Irregular and discontinuous periventricular bands are also common in ageing, but are also associated with other features of SVD and with periventricular venous collagenosis[30]. Punctate periventricular WMLs are frequently seen in ageing, even in people aged <50 years, can be of vascular or nonvascular origin, and are relatively stable over time[29]. Early confluent WMLs and confluent periventricular WMLs are less common than the previously mentioned features, but can progress faster, thereby mimicking the evolution of MS lesions, and are more strongly associated with vascular risk factors[31], lacunae[32] and clinical disability[33]. These age related and ischemic periventricular white matter changes have not been studied separately in MS, but are difficult to distinguish from periventricular MS lesions.

Widened Virchow–Robin spaces often are seen around the anterior commissure in early adulthood, and near the vertex in older people, and can also be present at the centrum semiovale in cerebral amyloid angiopathy[34]. In MS, however, widened Virchow–Robin spaces are more prevalent, particularly in high convexity brain areas[35], which might indicate a perivascular inflammatory component of the disease[36], or be an indirect marker of cerebral atrophy. Brain volume loss occurs at a higher rate (0.5–1% per year) in MS than in healthy ageing (0.1–0.3% per year)[37], although interpretation of volume loss at the individual level is difficult.

Patients with MS develop age-related changes and vascular comorbidities over time, and these factors can affect clinical outcomes. Indeed, disability in MS is strongly associated with age[38] and vascular risk factors[39,40]. Vascular risk factors are also associated with worse imaging outcomes in MS: smoking is associated with decreased whole brain volume, obesity is associated with increased T1-hypointense lesion volume, and arterial hypertension and heart disease are associated with decreased grey matter and cortical volumes[41]. The presence of vascular risk factors should, therefore, be considered when interpreting imaging results in patients with MS.

[H2] Differentiation from MS

[H3] Brain lesion distribution and lesion features

The location and shape of lesions (**Figure 2**), as well as their signal behaviour on different sequences[2,3,6,42], are useful in differentiating MS from SVD — lesions in the optic nerve, juxtacortical areas, periphery of the brainstem and the posterolateral cervical spinal cord indicate MS rather than SVD, as do lesions that are irregular in shape or appear as Dawson fingers.

WMLs in SVD spare the U-fibres, affect the central pons, and are associated with lacunae and microbleeds. Lacunae can be differentiated from black holes seen in MS (T1 hypointensities) by virtue of their similarity to cerebrospinal fluid (CSF) signals. Widening of Virchow–Robin spaces in the basal ganglia — known as état criblé – is usually abnormal but not seen in MS, and is typically associated with extensive WMLs owing to arteriolosclerotic SVD.

Cerebral microbleeds detected with SWI (T2*-weighted) imaging[43] reflect haemosiderin deposits in the vessel walls and are a marker of vasculopathy that is most commonly due to amyloid angiopathy (in which the microbleeds have a primarily lobar distribution) or simple arteriolosclerosis (in which they are primarily in the deep grey matter)[44,45] (**Table 2**). Microbleeds reported in patients with MS might have been due to concomitant vascular disease[46], as they were not observed when patients with vascular disease were excluded[47]; in general, the presence of microbleeds therefore indicates SVD. Cortical siderosis is frequently seen with SWI in amyloid angiopathy[48], but not in MS.

The presence of a WML central vein, identified as a hypointensity relative to the surrounding lesion on T2* or FLAIR* images and known as the central vein sign, is thought to be characteristic of MS lesions (**Fig. 2**). Optimized T2* protocols can detect central veins in ~80% of MS lesions at 3T, but a smaller proportion of SVD lesions have central veins: a cut-off of 45% is highly predictive in distinguishing between the two conditions[49,50]. However, visualizing all lesions is not practical in the clinical setting, and this cut-off might be less accurate in older patients with MS and vascular comorbidities[51].

Cortical lesions detected with 3T imaging protocols (T1, T2 and DIR) are well described as features of MS[52,53](**Figure 2)**. However, cortical microinfarcts (diameter <200 μm) occur in vascular disease and can be seen with DIR at 3T[54–56], but may be difficult to differentiate from MS cortical lesions in older patients with MS and/or patients with vascular risk factors.

Specific features of vascular disease depend on the underlying pathogenic process (**Tables 2 and 3)**. Cortical, subcortical and basal ganglia infarcts with restricted diffusivity, as well as haemorrhages, can be present in many diseases that affect the vasculature (Fig. 3). Additional features suggest certain diagnoses; for example, large diencephalic pseudotumoural lesions and cerebral venous thrombosis suggest neuro-Behçet syndrome[15], leptomeningeal enhancement suggests many types of vasculitis, dural masses suggest granulomatosis with polyangiitis (formerly Wegener granulomatosis)[57] , increased T1 signal intensity in the pulvinar and/or enlarged basilar artery diameters[58] suggest Fabry disease, and anterior temporal lobe pole and external capsular WMLs suggest cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[59] (**Fig. 3**). The presence of multiple focal or long segments of vessel narrowing (**Fig. 3**) and concentric vessel wall contrast enhancement[60] helps to distinguish medium and large cerebral vasculitis from MS[25,57]. Finally, the central vein sign, assessed with SWI, was less common among patients with some autoimmune disorders that affect the small vessels (present in 15% of lesions) when compared with patients with MS (present in 89% of lesions)[51].

[H3] Spinal cord lesions

Spinal cord MRI is included in the MS diagnostic criteria[2] and has a major role in the differential diagnosis, as incidental spinal cord lesions do not occur in normal ageing[61,62] or in typical SVD[63]. Spinal cord infarcts rarely cause diagnostic difficulties clinically or with MRI[64] (**Table 3**), though the risk factors for spinal infarcts seem to differ from those for cerebral infarcts (spinal cord infarction patients being younger, more often women and less affected by hypertension and cardiac disease that those with cerebral infarction)[65].

[H1] Migraine

Migraine affects ~10–15% of the general population[66]. WMLs that look similar to those associated with vascular disease on MRI, some of which have a periventricular location, are associated with migraine. Owing to the young age of presentation, these WMLs are a common cause of MS misdiagnosis[17], particularly as their appearance on MRI can fulfil the radiological criteria for MS[8,9]. Migraine-associated WMLs are typically small and nonconfluent in the deep white matter (sparing U-fibres), are more stable over time than MS lesions[66], and occur

adjacent to the body of the lateral ventricle less frequently than in MS[67]. The central vein sign might also be useful in differentiating migraine from MS: the median percentage of WMLs with the central vein sign was lower in migraine (22%) than in MS (84%), although there was some overlap (2 out of 10 migraine cases with 80%)[68]. Additionally, a simplified algorithm of central vein sign determination (in 3 white matter lesions only) has recently shown good accuracy in differentiating MS from migraine[69]. Another differentiating feature of migraine with aura is a higher prevalence of silent brain infarcts, particularly in the deep grey matter and cerebellum[70], than seen in MS. Finally, cortical[10] and spinal cord lesions[71] might be helpful in diagnosing MS, as these lesions do not occur in migraine.

[H1] Neuromyelitis optica spectrum disorders

The clinical phenotype of NMOSD can overlap with that of relapsing–remitting MS, although NMOSD has a predilection for the optic nerve and spinal cord — involvement of the latter is typically associated with a longitudinally extensive transverse myelitis (LETM). Nevertheless, a young female with NMOSD who initially presents with unilateral optic neuritis with poor recovery and a few WMLs is likely to be diagnosed with MS. The discovery that serum antibodies against AQP4 water channels (which are present on astrocyte foot processes) are present in 60–90% of patients with NMOSD has advanced the diagnostic criteria[72,73]. The most recent criteria[74] use a single term (NMOSD) to describe all patients, but divide patients into those who have anti-AQP4 antibodies in addition to clinical disease — for whom imaging criteria only need to be satisfied in those without attacks that involve the optic nerve, spinal cord or brainstem — and those who do not have anti-AQP4 antibodies, for whom diagnosis of NMOSD requires satisfaction of stricter imaging and clinical criteria. Further refinement of the criteria for antibody-negative NMOSD is likely, particularly because ~20% of patients with this condition are serum-positive for anti-MOG antibodies[75–79] and not all such anti-MOG patients fit into the current boundaries that define NMOSD[80].

In addition to the association with NMOSD, anti-MOG antibodies are present in more than half of children with ADEM[75,78,81,82] and, in a study published in 2017, was detected in all 14 children with multiphasic disseminated encephalomyelitis[83]. Although MOG-antibody

associated disease can be confused with MS (for example, in children)[84–86], the general consensus is that it represents a distinct disease[87], which can be monophasic or relapsing[14].

[H2] Imaging features similar to MS

The old doctrine that most patients with NMOSD will have normal brain MRI scans has now been proven incorrect. Between 43% and 70%[88] of patients have brain lesions at onset, 13% of patients with NMOSD fulfil the Barkhof criteria for MS at disease onset[12], and up to 42% might do so later in the disease[88], although this proportion seems to be lower among anti-AQP4 antibody positive cohorts[11,13] (**Table 1**).Nevertheless, periventricular WMLs[11], corpus callosum lesions[88], brainstem lesions and short spinal cord lesions (in 14% of initial transverse myelitis episodes[89]) can occur in anti-AQP4-antibody associated disease.

Antibody-negative NMOSD represents a heterogeneous group of disorders, and the overlap of clinical and imaging features in MS and NMOSD leads to considerable inconsistencies in the diagnosis and management of patients[90]. Identification of specific MS and NMOSD imaging features will play an important diagnostic role in this group of patients.

[H2] Differentiation from MS

[H3] Brain and optic nerve lesions

Lesions that are considered typical of NMOSD, despite the fact that they are found in a minority of anti-AQP4 antibody positive patients[91], are distinct from those seen in MS, and are located in areas of high AQP4 expression in the brain. These areas include periependymal areas that line the lateral, third and fourth ventricles, including diencephalic structures such as the thalamus, hypothalamus (**Fig. 4**), posterior pituitary, pineal gland and the brainstem, typically the area postrema[11,91,92]. Cloud-like, poorly marginated (**Fig. 4**) and so-called pencil-thin ependymal enhancement can be seen in NMOSD, and distinguish this condition from MS[93–95]. Anti-MOG antibody associated disease can present with typical ADEM[85] or NMOSD-like[96] brain features. Adults and children with anti-MOG antibody associated disease frequently having three or fewer brain lesions, which are characterized by a fluffy, cloud-like appearance and can involve the brainstem — often the pons and/or areas adjacent to the fourth ventricle — and, typically, the cerebellar peduncles[14,87,97] (**Fig. 4**).

In NMOSD callosal lesions, in contrast to MS (which are perpendicular to the ventricle wall), are often located immediately adjacent to the lateral ventricles, following the ependymal lining, and can exhibit a characteristic 'arch bridge pattern'[98]. Radial and spindle-shaped WMLs, lesions that involve corticospinal tracts, and — in rare cases — meningeal enhancement can occur in NMOSD[95,99], but not in MS.

A previous analysis of brain lesions showed that MS can be distinguished from anti-AQP4 antibody and anti-MOG antibody positive NMOSD by use of defined criteria: "at least one lesion adjacent to the body of the lateral ventricle and in the inferior temporal lobe; or the presence of a subcortical U-fibre lesion; or a Dawson's finger type lesion"[11,13]. Additionally, clinically silent lesion activity — defined as an annual increase in T2 lesion load — occurs in MS, but does not usually occur outside of relapses in NMOSD[100].

Cortical lesions occur in MS[101] but are typically absent in NMOSD[102], in keeping with the pathological findings[103]. Similarly, diffuse brain atrophy and diffuse cortical thinning is observed in MS, whereas patients with NMOSD exhibit a lower degree of brain atrophy[104], and cortical thinning in these patients is mild and limited to motor, sensory and occipital cortices[102]. Whether deep grey matter abnormalities, such as volume loss and abnormalities in grey matter MTR and DTI, exist and help to differentiate MS from NMOSD is less clear[100,102,105–109]. However, the thalamic atrophy seen in MS does not usually occur in NMOSD[92], and changes in thalamic subregional fractional anisotropy can distinguish NMOSD from MS with a sensitivity of 61% and a specificity of 92%[105].

In MS, the presence of widespread abnormalities in normal-appearing tissues is commonly accepted. In NMO, such changes seem to be limited to tracks that connect to lesions, such as the optic nerve and spinal cord pathways[100]. Abnormal white matter brain changes visible with DTI in NMOSD seem to be limited to the splenium of the corpus callosum and the posterior corona radiata — the latter was related to visual impairment[100] and to damage of the optic radiations[110] and corticospinal tracts[111]. Widespread white matter changes (beyond the optic radiations and the corticospinal tracts) in NMOSD were reported in one study, but the patients had not been tested for antibodies, and nonspecific MS-like brain lesions were not excluded in some patients[112].

A study of the central vein sign in NMOSD and MS showed that this feature is less common in anti-AQP4 antibody associated NMOSD (present in 32% of lesions) than in MS

(80% of lesions)[113]. A cut-off of 54% was suggested as a way to reliably distinguish between the two disorders[113].

Astrocyte damage occurs in NMOSD, whereas astrocytic activation and gliosis typically occur in MS, so myo-inositol values measured with MRS – a marker of astrocytic damage - could be useful for distinguishing between the conditions. Indeed, 3T MRS of spinal cord lesions revealed significantly lower myo-inositol values in patients who were positive for anti-AQP4 antibodies than in patients with MS and healthy controls. The findings also indicated a trend towards higher levels in patients with MS[114]. Of interest, levels of *N*-acetylaspartate — a marker of neuronal integrity — in lesions were significantly lower in patients with MS, than in healthy controls whereas only a nonsignificant trend towards a reduction was seen in patients who were positive for anti-AQP4 antibodies[115].

In contrast to MS, anti-AQP4 antibody associated optic neuritis is often associated with a long optic nerve lesion that tends to be more posterior and can extend into the optic chiasm. Bilateral optic neuritis is characteristic of anti-MOG antibody associated disease and tends to involve the anterior visual pathway with associated optic nerve head swelling[116,117].

[H3] Spinal cord lesions

LETM, a contiguous spinal cord lesion spanning three or more vertebral segments, is a characteristic feature of anti-AQ4 antibody associated transverse myelitis attacks. This feature is not specific, and is often seen in monophasic idiopathic transverse myelitis, in anti-MOG antibody associated disease (in which conus involvement is typical)[77,96], and in other inflammatory and noninflammatory spinal cord disorders, but it rarely occurs in MS[75,118]. Also in contrast to MS, central, symmetrical T1-hypointense spinal cord lesions that particularly involve central grey matter and often appear oedematous in the acute stages, are typical of NMOSD[91]. 'Bright spotty' T2 cord lesions also occur more commonly in NMOSD than in MS[119,120]. In the chronic stages of NMOSD, pronounced and extensive cord atrophy with or without T2 hyperintensity[121] and occasionally with syrinx-like cavities[122], can occur. LETM lesions that extend into the brainstem are more typical of NMOSD than of other causes of LETM[123].

The timing of spinal cord MRI in relation to the onset of symptoms is important for identification of LETM. Early imaging might miss a long lesion in evolution, whereas late imaging might show a shortening or entirely resolved lesion[89,121]. Thus because the early scan

performed for diagnostic reasons may not demonstrate the full extent of inflammation, further imaging may be indicated while the patients continues to deteriorate. Asymptomatic spinal cord lesions are less common in NMOSD than in MS, but gadolinium enhancement is present in the majority of, but not all, acute NMOSD transverse myelitis attacks[123,124]. The presence of ring-enhancing spinal cord lesions seems to be useful for distinguishing NMOSD from other causes of LETM, but not for distinguishing NMOSD from MS[125].

Besides lesions, cervical cord atrophy and MTR abnormalities are absent or much less prominent in patients with anti-AQP4 antibody associated disease than in patients with MS[100,104].

[H1] Other MS imaging mimics

The differential diagnosis for MS includes a long list of conditions, including other CNS inflammatory diseases, infections, neoplasms, and toxic, metabolic and hereditary disorders, all of which can present with WMLs — these conditions have been reviewed in detail elsewhere[3,5,6,18,57,126–128,59,129]. Exclusion of all MS mimics is not trivial [3], and a diagnosis of MS should be re-evaluated in the presence of an atypical clinical presentation or family history, childhood or juvenile onset of symptoms, onset with a slow isolated progressive paraplegia, dystonia, epilepsy or psychiatric disorders, peripheral nerve and extra-CNS involvement[5,59,130] together with specific MRI features and other paraclinical results (such as findings of serum and CSF analysis). Nevertheless, recognizing features that suggest alternative, often rare, diagnoses can be challenging, even for MS specialists. Whereas systematic identification of typical MS MRI features is incorporated into current MS diagnostic criteria, the approach to exclusion of alternative diagnoses is not standardized. In the following sections, we summarize key MRI features that suggest uncommon diseases associated with white matter lesions.

[H2] Brain lesions

[H3] Distribution

When considering brain MRI features, it is important to sequentially check each brain area, most importantly the white matter, white matter–grey matter junction, the grey matter and the brainstem.

Multiple WMLs that have poorly defined margins and are all the same age, usually not adjacent to the ventricles, indicate monophasic disorders such as ADEM[131]. This pattern is distinct from MS, for which lesions must be of different ages (disseminated in time) and chronic and are typically adjacent to the ventricles.

Bilateral, confluent and symmetrical WMLs that spare the U-fibres (which MS lesions do not) are characteristic of the inherited leukodystrophies (**Fig. 5**). WML distribution patterns and associated features can narrow the diagnostic options to identify specific leukodystrophies[59,129].

The observed pattern of corpus callosum involvement can suggest specific diagnoses. Central 'snowball' lesions are typical of Susac syndrome (**Fig. 5**)[132]. Extensive, symmetrical, poorly defined, bridge-like lesions indicate CNS lymphoma and glioblastoma[133]. Predominant involvement of the central layers of the corpus callosum suggests severe malnutrition and alcoholism[134].

The white matter–cortex junction should be carefully checked. Juxtacortical lesions (in U-fibres that abut the cortical ribbon) are typical of MS, but lesions that spread through the white matter—grey matter junction into the superficial layers of the cortex are uncommon in MS. Such lesions are seen in ADEM[131], infarcts (when lesions are typically wedge-shaped and point to the WM) (**Fig. 3**), GABA-A autoantibody disease (in which lesions usually have a fluffy appearance)[135], progressive multifocal leukoencephalopathy (in which lesions have a predilection for the frontal lobes and have sharp grey matter borders and ill-defined white matter borders; Fig. 5)[136–141], and mitochondrial encephalomyopathy, lactic acidosis stroke-like episodes syndrome (MELAS, in which lesions overlap between different vascular territories)[142]. PML lesions can be unifocal (particularly in the presymptomatic phase) or multifocal, and tend to be confluent at late stages of the disease. Lesions become increasingly hypointense over time on T1-weighted images (Fig. 5), and T2-weighted imaging can reveal a microcyst or granular pattern[143].

Cortical lesions can be seen in some systemic autoimmune disorders, such as systemic lupus erythematosus[144], and some inherited leukodystrophies, such as adult onset leukodystrophy[145], although not all[146]. However, the value of detecting cortical lesions with DIR in differentiating MS from other acquired and inherited disorders that affect the white matter is unknown.

Symmetrically distributed deep grey matter (thalamus and basal ganglia) lesions suggest ADEM[131,147], inherited metabolic and mitochondrial disorders[142], extrapontine myelinolysis[148], infection, and lymphoma[149]. MRI signal abnormalities in specific thalamic or hypothalamic areas can also indicate alternative diagnoses; for example, changes in the lateral geniculate body indicate X-linked adrenoleukodystrophy[150], changes in the mammillary bodies indicate thiamine deficiency[151], and changes in the hypothalamus and pituitary gland indicate sarcoidosis[152].

When diffuse, ill-defined brainstem involvement is predominant, CNS infections (such as listeriosis (**Fig. 5**) and Whipple disease), vasculitis and neoplasms should be considered[153]. A bias towards involvement of specific brainstem regions can also suggest specific diagnoses. In central pontine myelinolysis, which is associated with nutritional or electrolyte abnormalities, the lesions can (as in MS) be T2-bright, hypointense on T1-weighted sequences, and occasionally cause enhancement in the border regions, but their restricted lesion location, sparing of the ventrolateral pons, tegmentum and corticospinal tracts, gives a characteristic 'trident-shaped' or 'bat-winged' appearance[148]. Midbrain changes, such as the humming bird sign, have also been reported in globoid cell leukodystrophy and periaqueductal grey matter changes have been described in Leigh disease[59,129]. Brainstem pial FLAIR hyperintensity and tadpole atrophy (atrophy of the medulla and spinal cord with relative sparing of the pons) is seen in type II (late-onset) Alexander disease[154]. Finally, cerebellar dentate nucleus hyperintensities are typical of cerebrotendinous xanthomatosis[155] (**Fig. 5**).

[H3] Features and enhancement patterns

Tumefactive lesions are uncommon in MS. An open ring enhancement that points towards the grey matter is seen more frequently in demyelination than with tumours, but this feature is not specific[156]. Lesion expansion over time and persistent oedema should alert physicians to other possible diagnoses, such as neoplasms. Cerebral lymphoma characteristically presents with lesions that cause vivid, homogeneous enhancement, which might be present simultaneously in all lesions, can persist, and can be associated with restricted diffusivity. Furthermore, areas that are enhanced on MRI appear hypodense on unenhanced CT images for 93% of demyelinating lesions but only for 4% of tumours, suggesting that comparing

results of the two imaging tests is useful in distinguishing between diagnoses[157]. CT of the brain can also reveal calcifications that are characteristic of specific infections (such as toxoplasmosis) and metabolic disorders[3,158].

Punctate and curvilinear enhancing lesions in the pons are typical of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)[159]. Punctate enhancing lesions visible on T2-weighted or T1-weighted contrast-enhanced images have also been observed in patients with early natalizumab PML[138]. Linear contrast enhancement, particularly that which follows specific tracts, can feature in some inherited leukodystrophies, such as X-linked adrenoleukodystrophy[59].

Cavitations are not common in MS but can be observed in inherited leukodystrophies (such as vanishing white matter disease, in which cavitations typically have an anterior location[150]) and in mitochondrial disorders, in which they are in the cerebral and cerebellar white matter[59,142]. Spectroscopy can help to differentiate MS from mitochondrial diseases: a characteristic lactate peak is present in mitochondrial disease but not in MS[142].

Leptomeningeal enhancement seen with MRI is a red flag that indicates CNS infection (for example, Lyme disease, *Brucellosis*), sarcoidosis, vasculitis or Susac syndrome as possible alternative diagnoses[160,161]. Cranial nerve enhancement (**Fig. 5**) — except for the optic nerve and initial portion of the trigeminal nerves[162] — and spinal root enhancement are not seen in MS but do occur in CNS infection and sarcoidosis[163]. Post-contrast T2-weighted FLAIR MRI can detect small foci of leptomeningeal inflammation in MS, which might prove to be useful in distinguishing MS from noninflammatory white matter conditions[164].

[H2] Spinal cord lesions

An LETM with gadolinium enhancement and cord swelling owing to oedema is another important red flag, that indicates an alternative diagnoses such as NMOSD, ADEM, sarcoidosis (**Fig. 5**) and infections must be considered[64,152]. Spinal cord sarcoidosis predominantly affects the thoracic segments; central canal enhancement alone or in combination with dorsal subpial enhancement, resembling a trident (**Fig. 5k**), has been reported[165]. Spondylosis might be confounded with MS. Transverse pancake-like gadolinium enhancement that is associated with and just caudal to the site of maximal stenosis and is at the rostrocaudal midpoint of a spinal cord spindle-shaped T2 hyperintensity suggests that spondylosis is the cause of

myelopathy[166]. Spinal cord lesion enlargement, nodules, haemorrhage and cavitations are atypical in MS, but can feature in neoplasms, sarcoidosis and infections[167].

Vitamin B12 deficiency and copper-deficiency-associated myelopathy cause demyelination of long fibre tracts (spinal dorsal and lateral columns, and brain pyramidal and spinocerebellar tracts). These conditions result in T2 hyperintensities that are usually symmetrical in axial sections, so good-quality axial imaging is needed for an accurate diagnosis[168–170].

[H2] Single lesion or absence of lesions

In a patient with a clinical course that indicates primary progressive MS, a single demyelinating lesion in the spinal cord, brainstem or cerebral white matter could indicate progressive solitary sclerosis[171]. In the presence of single lesions, particularly if increasing in size over time, brain tumours and infection should be considered/excluded[3]. Similarly, a normal brain and spinal cord MRI is rare in patients with MS, so if a patient presents with clinical symptoms of MS but no detectable lesions, alternative diagnoses should be considered. Such diagnoses include hereditary spastic paraparesis, and metabolic disease, such as vitamin B12 or copper deficiency.

[H1] Summary of imaging differentiators

In summary, specific MRI features can help to make alternative diagnoses when MS is suspected[128] (**Tables 2 and 3)**. Macrobleeds or microbleeds, infarcts, WMLs that spare the U-fibres and siderosis suggest cerebrovascular disease. Extensive spinal cord lesions are useful in distinguishing NMOSD from MS, and the presence of meningeal enhancement, increasing lesion size over time, calcifications, complete ring enhancement and strictly symmetrical WMLs suggest diagnosis other than MS. These features should be systematically excluded, and we suggest the simple mnemonic 'iMIMICS' to represent the imaging red flags. The mnemonic stands for: patterns of meningeal (M) enhancement; indistinct (I) border or increasing (I) lesion size; the presence of macrobleeds (M) or microbleeds (M); the presence of cortical or lacunar **i**nfarcts (I); the presence of cavities (C) complete (C) ring enhancement or calcifications (C); and **s**ymmetrical (S) lesions, lesions that spare (S) the U-fibres, siderosis, and **s**pinal (S) cord extensive lesions (**Table 4**). However, in a population for whom the prior

likelihood of MS is high, the clinical picture is much more sensitive and specific for refuting the diagnosis of MS than is the presence of MRI red flags[172].

[H1] Conclusions

In this Review, we suggest a diagnostic algorithm **(Fig. 1**) that incorporates the current MS diagnostic criteria, features that have been identified as useful in differentiating MS from NMOSD, and imaging features that suggest other alternative diagnoses. Although this algorithm is intended to promote homogenization of a differential diagnostic approach, its ability to improve the specificity of MRI still needs to be tested.

Several challenges remain. First, MS commonly coexists with disorders (such as migraine and cerebrovascular disease) that can have a similar appearance on MRI, and its interaction with and separation from these disorders warrants further studies. Such studies can be done only with cohorts of MS patients for whom comorbidity data are clearly documented, and cohorts of appropriate controls. Therefore, the ability of the current MS diagnostic criteria to differentiate between MS and other conditions in patients without CIS requires validation. Direct comparison between disorders was a useful approach in determining imaging features that differentiate between MS, NMOSD with brain involvement[11] and migraine[67], but comparative studies are lacking in many other neurological diseases that mimic MS. Third, differentiating MS from mimics relies on good clinical and neuroradiological expertise, along with the ability to perform high-quality and state-of-the-art MRI protocols — such expertise are often not available outside specialized research centres. The use of pulse sequences, such as SWI and DIR, which are usually not done in routine clinical scans, enabled identification of the central vein sign and cortical lesions, promising MRI measures that could have a role in the diagnostic criteria of MS[10,51] and might help to identify features of other disorders, such as microbleeds in SVD. Finally, owing to the rarity of some MS mimics, the evidence for differentiating features of these conditions comes from case reports and series and thus the reliability of these discriminators is unknown. Direct comparative studies with larger number of cases would clarify their accuracy.

Despite these challenges, most typical MS patients are diagnosed accurately and speedily, particularly in areas of the world in which MS is common. Nevertheless, many people with unconventional clinical features might still have MS. Incorporating the differentiating imaging features described in this Review into the diagnostic process should

improve diagnostic accuracy. Importantly, the neurologist should also maintain an open mind when following up patients who have been diagnosed with MS but who have atypical clinical or imaging features.

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The most recent MS criteria and the role of MRI in documenting dissemination in time and space are discussed.

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This paper describes the brain imaging criteria that were found to be useful in differentiating MS from NMOSD)

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A good introduction to the problem of MS misdiagnosis

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Key points

- MRI plays a crucial role in the diagnosis of multiple sclerosis (MS) by revealing the dissemination in space and time of white matter lesions (WMLs), as well as helping to rule out alternative diagnoses
- WMLs with a similar distribution to that seen in MS can occur in many disorders, from common age-related vascular disease and migraine, to neuromyelitis optica spectrum disorders and rarer conditions
- The distribution of WMLs can help to differentiate MS from antibody-mediated CNS disorders
- The proportion of lesions with the central vein sign and the presence of cortical lesions can be useful in differentiating MS from some of its mimics
- Meningeal enhancement, indistinct (ill-defined), increasing lesions over time, macro and microbleeds, infarcts, cavities, symmetrical lesions that spare the U-fibres, siderosis and extensive spinal cord lesions suggest diagnoses other than MS.
- We suggest the mnemonic iMIMICs to remember the atypical MRI features that point to a diagnosis other than MS.

Glossary

Lacunae - small (3-15 mm diameter) round or ovoid subcortical infarcts in the territory of one perforating arteriole with MRI signal similar to CSF

Perivascular spaces - spaces that follow the course of a vessel as it goes through grey or white matter. The spaces have signal intensity similar to CSF on all sequences. They appear linear when imaged parallel to the course of the vessel, and round or ovoid, with a diameter generally smaller than 3 mm, when imaged perpendicular to the course of the vessel.

Dawson fingers - elongated MS plaques through the corpus callosum and perpendicular to the lateral ventricles

U-fibres - short association fibres, represent connections between adjacent gyri of the brain, located within the cortex or immediately deep to it in the very outer parts of the subcortical white matter

Table 1 | Studies showing fulfilment of MS diagnostic criteria for DIS by other neurological disorders. Disorder	**No. of patients**	**% patients that meet criteria**		**Reference**
		Barkhof criteria	**McDonald 2010 criteria**	
Migraine	44	NA	9	8
	168	7.1	34.5	7
	32	NA	34	9
Anti-AQ4 antibody associated NMOSD	31	12.9	NA	12
	26	15.9	NA	10
	67	13	NA	11
Anti-MOG antibody associated NMOSD	21	14.3	NA	12
	26	26.9	NA	13
Neuro-Behçet disease	84	13.1	NA	14
Primary CNS vasculitis	24	50	NA	15
Secondary vasculitis	25	58	NA	15
SLE or Sjogren syndrome	16	17	NA	15

Data are from a limited number of studies in which the MS imaging criteria were explored in other conditions. The findings support the view that these criteria should not be used in isolation. AQP4, aquaporin 4; DIS, dissemination in space; MOG, myelin oligodendrocyte; NA, not available; NMOSD, neuromyelitis optica spectrum disorder; SLE, systemic lupus erythematosus.

Table 2 | Differentiation of cerebral small vessel disease from MS with MRI

Small vessel disease type		Differentiating features
Arteriosclerotic or related to age and vascular risk factors		Lesions (microbleeds, lacunae) in perforating art territory (basal ganglia, brainstem) Symmetrical, poorly demarcated deep WMLs tha U-fibres Central pontine diffuse white matter changes an infarcts Spared spinal cord
Cerebral amyloid angiopathy (sporadic and hereditary)		Lobar microbleeds and macrobleeds, convexity subarachnoid haemorrhages and/or cortical side
Inherited or genetic[a]	CADASIL	WMLs in the external capsule and temporal pole lacunae in the basal ganglia and central pons
	COL4A1 mutations	Arterial dilatation and/or aneurysms, porencepha microbleeds
	Fabry disease	Vertebrobasilar arterial dolicoectasia, pulvinar T hyperintensity, infarcts
Inflammatory or immune-mediated	Systemic vasculitis with cerebral involvement (for example, ANCA positive vasculitis) Infectious vasculitis Vasculitis associated with connective tissue disorders	Meningeal enhancement Lacunae, microbleeds, territorial infarcts, pseudotumoural lesions in the basal ganglia and brainstem Longitudinal extensive transverse myelitis
Other (for example, post-radiation angiopathy)		Diffuse WMLs, sometimes with cavitation owing coagulative necrosis; distal artery thinning detec with angiography

Vascular disease incorporates many different disorders, so identifying features that point to the specific small vessel diseases and differentiate from MS is helpful. [a]Only some examples given: for more information, see Pantoni et al.[25]. ANCA, anti-neutrophil cytoplasmic antibody; CADASIL, cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy; WML, white matter lesion.

Table 3 | MRI observations that differentiate between multiple sclerosis and the indicated disorders

MRI observations [		**Possible disorders**
Brain		
Lesion location	Central and diencephalic (thalamus, basal ganglia, hypothalamus)	NMOSD, other autoantibody-mediated diseases (for anti-MA2 antibody encephalopathy[173]), ADEM, Susac neurosarcoidosis, infection (for example, Whipple dis metabolic disorders (for example, hyponatraemia, th deficiency), mitochondrial disorders
	Adjacent to third and fourth ventricles or aqueduct, area postrema	NMOSD
	Involving or following corticospinal tracts	NMOSD, HTLV, globoid cell leukodystrophy
	Lack of temporal and lateral ventricle lesions, lack of Dawson fingers or lack of S-shaped U-fibre lesion	NMOSD, migraine, inherited leukodystrophies
	Posterior limb of internal capsule ("string of beads")	Susac syndrome
	Lateral geniculate body or optic radiations	Adrenoleukodystrophy
	Central pons	SVD, metabolic (for example, hyponatraemia)
	Brainstem pial FLAIR hyperintensity, tadpole atrophy (atrophy of the medulla and spinal cord with relative sparing of the pons)	Type II (late onset) Alexander disease[154]
	Crescent-shaped lesions involving the middle cerebellar peduncles and adjacent pontine white matter	Progressive multifocal leukoencephalopathy
	Dentate nucleus (T2 hyperintensities)	Cerebrotendinous xanthomatosis
	Bilateral occipital white matter	PRES, X-linked [adrenoleukodystrophy, globoid cell leukodystrophy
Lesion characteristics	Cerebrospinal fluid-like signal intensity	Dilated Virchow–Robin spaces
	Indistinct margins	NMOSD, ADEM, other antibody-mediated encephalo example, anti GABA-A)
	Symmetrical lesions	NMOSD, ADEM, migraine, inherited leukodystrophie
	Punctate (<5 mm diameter), rarely confluent lesions	Migraine, SLE
	Oedematous and marbled callosal lesion, with or without extension into cerebral hemispheres or the 'arch bridge sign' the name given to the lesion described	NMOSD, lymphoma
	Central 'snowball'-shaped callosal lesion	Susac syndrome
	Callosal thinning	Adult-onset autosomal dominant leukodystrophy, va white matter disease, Susac syndrome
	Extensive, confluent, tumefactive hemispheric white matter lesions	NMOSD, cerebral vasculitis, neuro-Behçet disease, in cancer
	Unusual enhancing patterns — poorly marginated, patchy, cloud-like, rare meningeal or linear of ependymal lateral ventricles	NMOSD, neurosarcoidosis, cancer
	Associated with silent infarcts and/or microbleeds	Migraine, dilated Virchow–Robin spaces, cerebral vas Susac syndrome, CADASIL, COL4A1, Fabry disease, fa
	Associated with convexity haemorrhage	Reversible vasoconstriction syndrome in association cerebral amyloid angiopathy
	Associated with cranial nerve and leptomeningeal contrast enhancement	Cerebral vasculitis, Susac syndrome, neurosarcoidosi (for example, neuroborreliosis)
	Associated with dural masses	Neurosarcoidosis, cerebral vasculitis (for example, GI
Lesion activity	None between relapses, or rare new lesions	NMOSD, ADEM, migraine
	Absence of contrast enhancement	Migraine, dilated Virchow–Robin spaces
	Punctate and curvilinear enhancement lesions in the pons	CLIPPERS
	Linear perivascular radial gadolinium enhancement, extending outward from the ventricles and in the cerebellum	Glial fibrillary acidic protein antibody disease[164]
Optic nerve		
Lesion characteristics [	Long lesion, bilateral	NMOSD
	Posterior, chiasmatic	Anti-AQP4 antibody associated optic neuritis

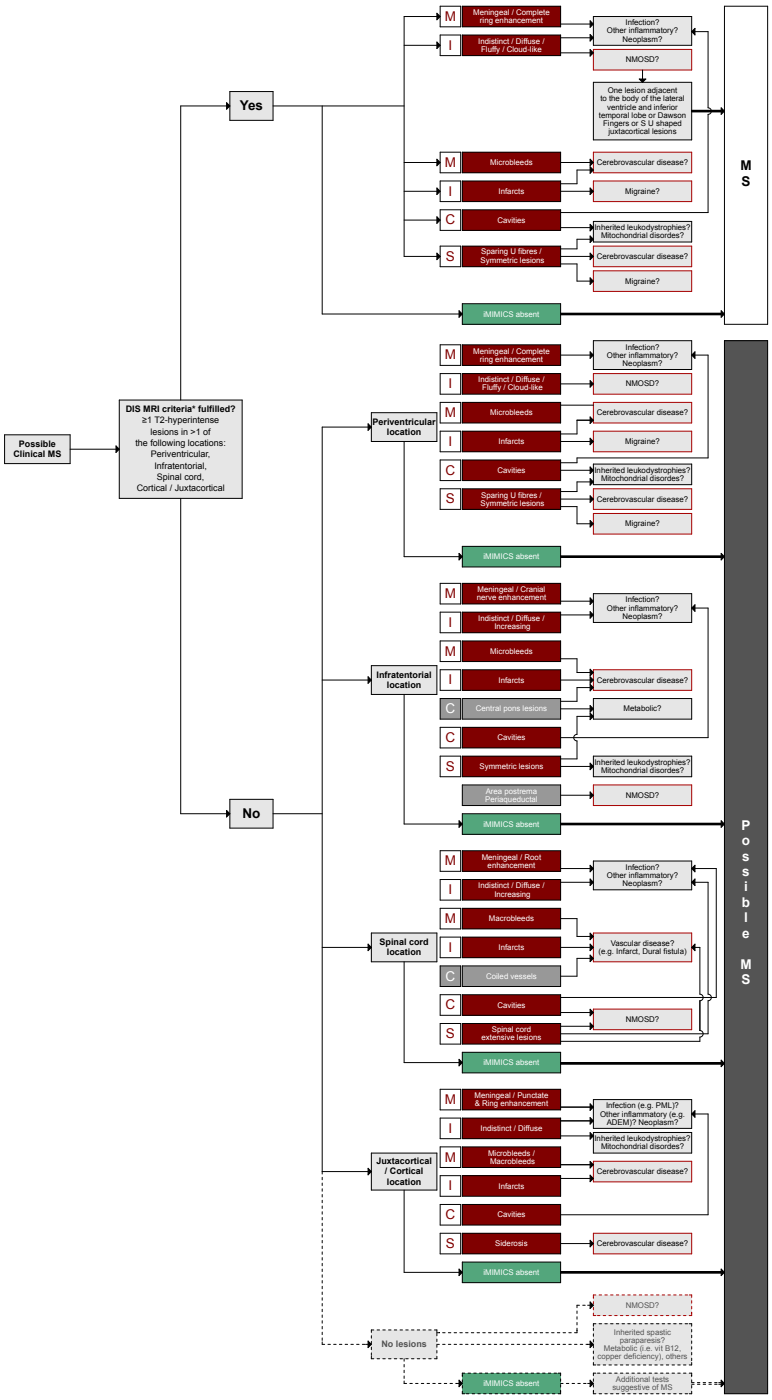
	Long lesion, anterior	Anti-MOG antibody associated optic neuritis
Spinal cord		
Lesion location	Conus involvement	Anti-MOG antibody-associated transverse myelitis
	Thoracic involvement	NMOSD, HTLV-1 myelopathy, arteriovenous fistulae
	Centrally symmetrically placed with grey and white matter involvement	NMOSD
	Posterior columns or spinothalamic tracts	Metabolic (for example, vitamin B12, Cu^{2+} deficiency) (for example, HIV, *Treponema pallidum*), adrenoleuk DARS-associated encephalopathy[174]
Lesion characteristics	T1 hypointensity	NMOSD
	Bright spotty lesions	NMOSD
	Patchy nodular or central canal contrast enhancement, trident sign	Neurosarcoidosis
	Pencil-like, 'snake-like' or 'owl's eye' T2 hyperintensities of the anterior horns of the grey matter on axial images, associated with T2 hyperintensities of the dorsal part of the vertebrae in the affected region	Spinal cord infarction
	T2 increased peri-medullary flow voids, vascular	Dural arteriovenous fistulae
	Pancake-like gadolinium enhancement or spindle-shaped lesion	Spondylotic myelopathy
	Nerve root and leptomeningeal contrast enhancement	Neurosarcoidosis, infection
	Lesion that affects ≥3 vertebral segments	NMOSD, ITM, ADEM, SLE, Sjogren syndrome, neuro-B disease, neurosarcoidosis, spinal cord infarction, dura arteriovenous fistulae, paraneoplastic, spondylotic m glial fibrillary acidic protein antibody disease[164]
	No lesions	Migraine, dilated Virchow–Robin spaces, SVD
Magnetic resonance angiography, non-conventional or quantitative imaging		
Imaging characteristics	Multiple arterial stenosis and post-stenotic dilatations and/or vessel wall contrast enhancement	Cerebral vasculitis, infection (for example, varicella z
	Lack of diffuse non-lesion tissue damage	Anti-AQP4 antibody associated disease, neuroborreli
	Absence of thalamic atrophy	NMOSD
	Absent cortical lesions	NMOSD, migraine
	Absence or minority of central vein sign	Susac syndrome, migraine, NMOSD, ADEM
	Reduced myo-inositol or creatinine in lesions	Anti-AQP4 antibody associated transverse myelitis
	Reduction of *N*-acetyl aspartate	Adrenoleukodystrophy
	Lactate peak	Mitochondrial disorders

Not all possible differential diagnoses of multiple sclerosis are included, but only those that have been reported to mimic multiple sclerosis. ADEM, acute disseminated encephalopathy; AQP4, aquaporin-4; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; COL4A1, collagen type IV alpha 1 mutations; GPA, granulomatosis with polyangiitis; HIV, human immunodeficiency virus; HTLV, human T cell lymphotropic virus type 1; ITM, idiopathic transverse myelitis; MOG, myelin oligodendrocyte; MS, multiple sclerosis; NMOSD, neuromyelitis spectrum disorder; PRES, posterior reversible encephalopathy syndrome; SLE, systemic lupus erythematosus; SVD, small vessel disease.

Table 4 | Imaging features indicated by the iMIMICs mnemonic and the MRI sequences required to identify each feature

Letter	Meaning	Minimum essential MRI sequences
M	Meningeal enhancement	2D axial or 3D contrast-enhanced T1-weighted
I	Indistinct lesions Increasing lesions	Saggital 2D or 3D T2-FLAIR [
M	Macrobleeds Microbleeds	2D axial T2*-weighted gradient echo
I	Infarcts	2D axial, 3D T1-weighted and DWI
C	Cavities Complete ring enhancement	2D axial or 3D contrast-enhanced T1-weighted
S	Symmetrical lesions Sparing of U-fibres	2D axial or coronal or 3D FLAIR
	Siderosis	2D axial T2*-weighted gradient echo or FLAIR
	Spinal cord extensive lesions	Sagittal dual-echo (proton-density and T2-weighted) and/or fast spin-echo, contrast-enhanced T1-weighetd spin-echo, axial 2D and/or 3D T2 and contrast-enhanced T1-weighted fast spin-echo

DWI, diffusion-weighted imaging; FLAIR, fluid attenuation inversion recovery.



DIS – Dissemination in time, NMOSD – neuromyelitis spectrum disorder, MS – multiple sclerosis, ADEM – acute disseminated encephalopathy.

*MS diagnostic criteria 2017[172] require DIS with documentation of 2 of the 4 categories shown in the box but also Dissemination in Time or CSF-specific oligoclonal bands.

Figure 1 | Use of the iMIMICs mnemonic in the differential diagnosis of multiple sclerosis using MRI If the criteria for dissemination in space (DIS) are not met because lesions are present in only one of the required locations (alone or with other lesions in nondiagnostic locations)4, other diagnoses should be considered according to the imaging features

observed. Dissemination of lesions in time or the presence of oligoclonal bands is required to make the diagnosis in the absence of a better explanation. Even when the DIS criteria are met, other diagnoses can be considered. Having no brain or spinal cord lesions is rare and should be seen as a special case (dashed lines) in which complementary tests other than MRI are needed to support the diagnosis. ADEM, acute disseminated encephalopathy; NMOSD, neuromyelitis spectrum disorder; PML, progressive multifocal leukoencephalopathy.

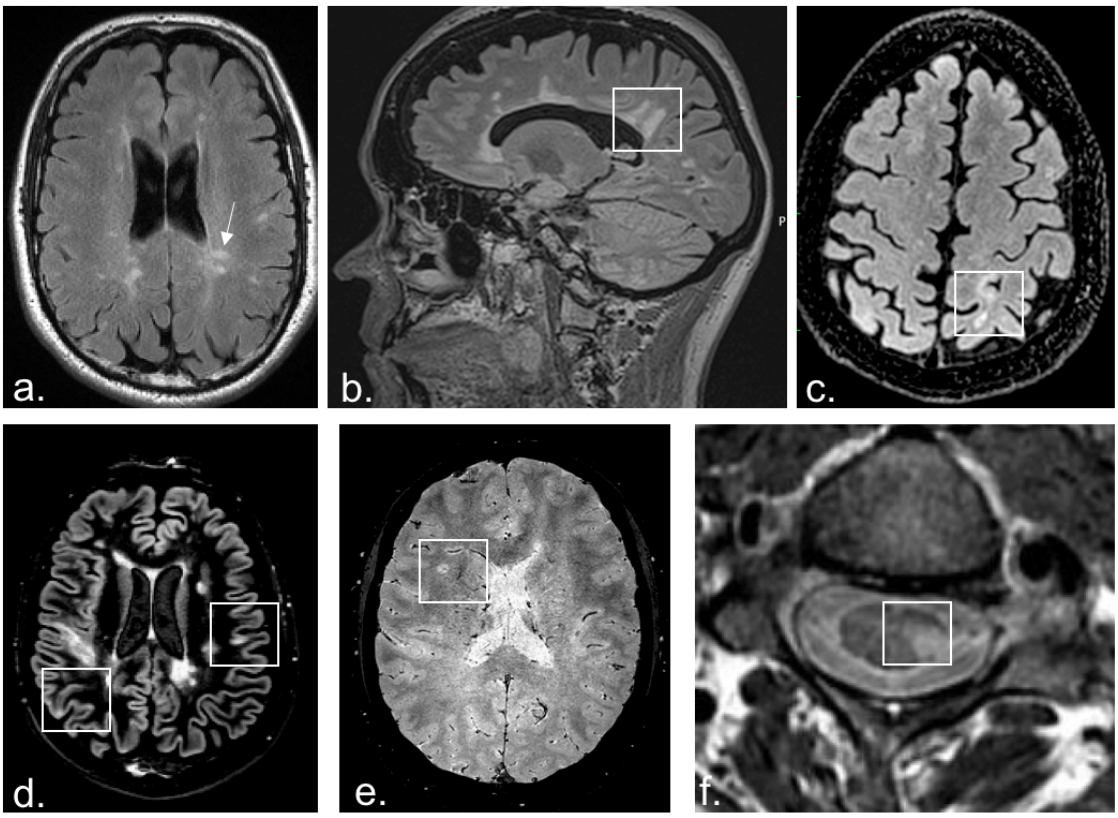


Figure 2 | Typical imaging features of multiple sclerosis with conventional MRI and possible differentiating features with non-conventional MRI. a | So-called Dawson fingers (arrow), visible as ovoid periventricular hyperintense lesions perpendicular to the body of the lateral ventricle and/or to the callosal junction, shown in an axial FLAIR image. b | Dawson fingers (box) showing in a sagittal FLAIR image. c | an S-shaped juxtacortical lesion (box) in an axial FLAIR image. d | Cortical lesions (boxes) shown in an axial Double Inversion Recovery (DIR) image. e | The central vein sign, a hypointensity relative to a surrounding hyperintense lesion visible on susceptibility-weighted imaging (an axial T2* image). f | Eccentric short spinal cord lesions that are typical of MS, shown in an axial T2-weighted image

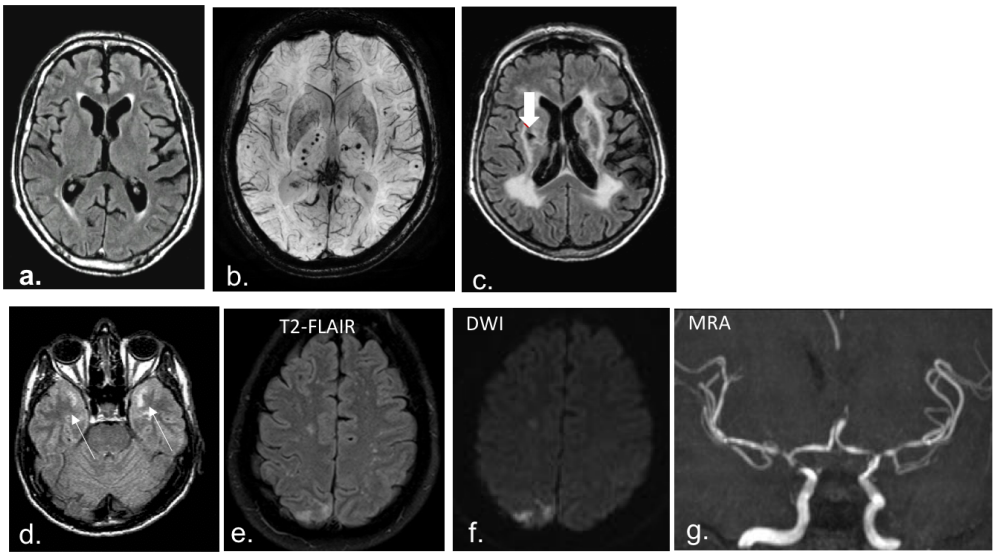


Figure 3 | Age-related white matter lesions and cerebrovascular disease lesions. a | Axial FLAIR brain MRI showing periventricular pencil-thin lining hyperintensities and bilateral, symmetrical caps lining the frontal horns of the lateral ventricles (arrow), features that are commonly seen in normal ageing. b | Microbleeds associated with small vessel disease (SVD), depicted in an axial gradient-echo T2*-weighted image as rounded hypointensities in the basal ganglia (arrows) and the cortex. c | An axial FLAIR image showing periventricular white matter hyperintensities that spare the U-fibres and lacunar infarcts in the deep white matter and grey matter (arrow), associated with SVD. d | Temporal pole white matter hyperintensities (arrows) associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), shown in an axial FLAIR image. e | Hyperintense white matter lesions in multiple vascular territories, which are typically associated with cerebral vasculitis. F | Wedge-shaped cortical infarcts (arrow) that are usually associated with the white matter lesions in cerebral vasculitis, shown in diffusion-weighted images. g | Bilateral middle cerebral artery segmental stenosis (arrows) depicted in a magnetic resonance angiogram.

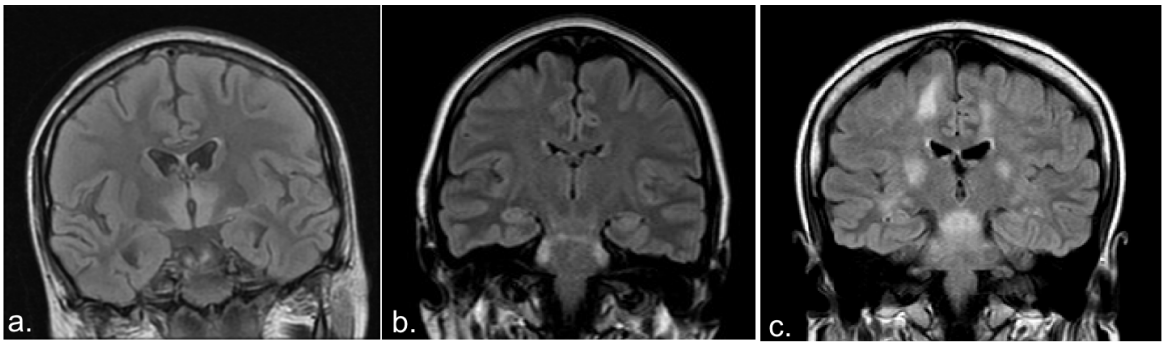


Figure 4 | Neuromyelitis optica spectrum disorder brain lesions a | Coronal fluid attenuation inversion recovery (FLAIR) image from a patient who was positive for anti-aquaporin-4 antibodies. Bilateral diencephalic hyperintense lesions are visible (box). b | Coronal FLAIR images from patients who were anti-myelin oligodendrocyte glycoprotein antibodies. Fluffy, poorly demarcated lesions with bilateral involvement of the middle cerebellar peduncles are shown on the left (box), and bilateral cloud-like lesions in the deep white matter are shown on the right (arrows)**.**

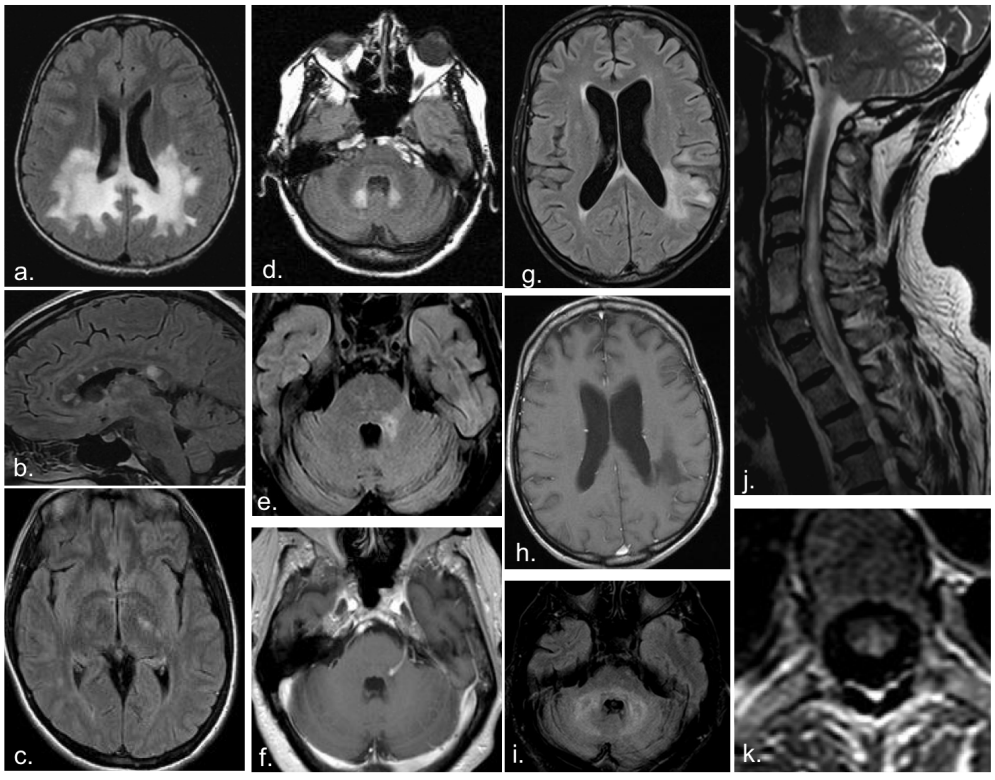


Figure 5 | Imaging features of other multiple sclerosis mimics. a | Axial fluid attenuation inversion recovery (FLAIR) image showing features of the inherited leukodystrophies. Bilateral, confluent and symmetrical white matter lesions that spare the U-fibres (unlike in multiple sclerosis) are typical, and the predominantly posterior distribution shown is typical of X-linked adrenoleukodystrophy (arrows). b | Images of the typical features of Susac

syndrome: intracallosal snowball-shaped T2-FLAIR hyperintense lesions (top), and lesions in the posterior limb of the internal capsule, appearing as as a ‘string of beads’ in an axial FLAIR image (arrows). c | Bilateral T2-FLAIR hyperintensities (arrow) in the dentate nucleus, a feature of cerebrotendinous xanthomatosis. d | Imaging features of listeriosis. Diffuse, indistinct brainstem lesions with pons and left middle cerebellar peduncle (arrow) involvement is visible in an axial FLAIR image (top), and extensive left trigeminal nerve contrast enhancement (arrow) is seen with T1 post-contrast axial MRI (bottom). e | Imaging features of progressive multifocal leukoencephalopathy (PML). T2-FLAIR imaging reveals hyperintense lesions that typically involve the grey matter–white matter transition, with sharp lesional borders in the grey matter and ill-defined borders in the white matter. Such lesions appear as hyperintensities (arrow) with axial FLAIR imaging (top) and as hypointensities (arrow) with T1-weighted imaging (middle). Crescent-shaped lesions involving the middle cerebellar peduncles and adjacent pontine white matter (box) also occur in PML, visible with axial FLAIR imaging (bottom). f | Imaging features of sarcoidosis. Longitudinally extensive spinal cord lesions (box) can be seen in a sagittal T2-weighted cervicothoracic spinal cord scan (top). Central canal enhancement alone or in combination with dorsal subpial enhancement — known as the trident sign (arrow) owing to its resemblance to a trident — is also a feature of spinal cord sarcoidosis, illustrated in a thoracic cord axial post-contrast T1-weighted image (bottom).

Competing interests statement

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