Spinal cord involvement in multiple sclerosis and neuromyelitis optica spectrum disorders

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Spinal cord involvement is an important cause of disability in patients with multiple sclerosis or neuromyelitis optica spectrum disorders (NMOSDs). Multiple sclerosis and NMOSDs can be distinguished from other disorders that cause myelopathy by results from laboratory and radiological investigations. However, limitations in the sensitivity and specificity of spinal cord imaging and poor correlation with disability megasures have impeded the understanding of the relationship between spinal cord involvement and clinical manifestations. Nevertheless, studies of the pathological features of multiple sclerosis and NMOSDs have shown that quantitatively different mechanisms lead to differences in clinical course and pattern of accrual of permanent disability in the two disorders. Better understanding of these mechanisms is necessary to develop more informative clinical measures, electrophysiological methods, fluid biomarkers, and imaging techniques to detect and monitor spinal cord involvement in the diagnosis and management of patients with multiple sclerosis or NMOSDs, and as outcome measures in clinical trials.

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See Online for appendix

Introduction

Spinal cord involvement is common in multiple sclerosis and neuromyelitis optica spectrum disorders (NMOSDs) and is an important contributor to disability.[1,2] However, spinal cord pathology has been difficult to detect, characterise, and quantify because of limitations in the sensitivity and specificity of clinical outcome measures (eg, Expanded Disability Status Scale [EDSS] and Multiple Sclerosis Functional Composite [MSFC]) and spinal cord MRI. These limitations have impeded efforts to correlate spinal cord involvement with clinical manifestations and to integrate measures of spinal cord involvement as prognostic and outcome measures in clinical practice and research studies.[3]

Several developments have advanced our understanding of spinal cord involvement in multiple sclerosis and NMOSDs. The 2017 revisions of the McDonald criteria for the diagnosis of multiple sclerosis[4] re-emphasised the relevance of clinical and MRI manifestations that indicate spinal cord involvement to fulfil temporal or spatial dissemination. New methods to analyse gait and balance now allow more comprehensive assessment of impaired mobility, a key consequence of spinal cord involvement, than that provided by traditional clinical outcome measures.[5,6] Diagnostic biomarkers, such as antibodies against aquaporin-4 (AQP4) have improved delineation of the clinical and pathological features of NMOSDs and their differences to multiple sclerosis.[2] The quantification of neurofilament light chain (NfL) concentration in CSF and blood has emerged as a useful biomarker of axonal damage also in the spinal cord, facilitating disease monitoring.[7] Finally, new MRI techniques assessing the spinal cord show promise to elucidate correlations between clinical manifestations and pathology, and for use as clinical trial outcomes.[3]

This Review critically evaluates clinical and radiological manifestations of spinal cord involvement in multiple sclerosis and NMOSDs; appraises clinical measures, electrophysiological methods, biomarkers, and imaging to detect and quantify spinal cord involvement; provides best practices for incorporating spinal cord imaging to assist with diagnosis and as a clinical trial outcome measure; considers aspects of the pathophysiology of multiple sclerosis and NMOSDs that might explain differences in how disability accrues; and identifies key gaps in knowledge and areas for future research.

Clinical assessment of spinal cord involvement

Clinical manifestations reflecting spinal cord involvement are common in patients with multiple sclerosis or NMOSDs.[1] Motor impairment of the upper and lower extremities caused by weakness, incoordination, or sensory loss, and gait impairment are characteristic of spinal cord involvement in multiple sclerosis and NMOSDs.[1] Both the EDSS and MSFC, the most commonly used measures of disability in multiple sclerosis,[8] capture neurological manifestations that localise to the spinal cord.[1] Neither has been validated in NMOSDs. The Opticospinal Impairment Score is an ordinal scale that quantifies impairment of the optic nerve and spinal cord in NMOSDs.[9] This scale is not widely used, and its psychometric properties have not been studied in these disorders. The American Spinal Cord Injury Association Impairment Scale, a widely used ordinal scale to assess spinal cord injury,[10] might be helpful to assess patients with NMOSDs. Quantitative measurements, potentially more sensitive to spinal cord involvement than EDSS and MSFC, include grip strength measured with a dynamometer and assessment of postural stability,[11] but these measures are not commonly used in clinical practice or in clinical trials. Neither of these measures has been fully validated, particularly for longitudinal assessment.

Gait impairment, a common sequel of spinal cord involvement, is quantified in the EDSS by evaluating the distance a patient can walk and the assistance device they require, whereas in the MSFC it is quantified by the Timed 25-Foot Walk, a test of short-distance walking speed.[8] Measures of other aspects of mobility include the

Timed Up and Go Test (ability to rise from sitting to standing, walk a short distance, and turn), 2-minute and 6-minute walk tests (speed and endurance over an intermediate distance), and Multiple Sclerosis Walking Scale-12 (a patient self-report measurement of walking ability).[8] Formal analysis of gait requires specialised technology but is more sensitive to mild changes in gait and response to interventions than standard neurological testing,[5] sometimes detecting subtle disturbances in gait or balance in patients with multiple sclerosis before they are apparent clinically.[5] The sensitivity of gait analysis might be increased by assigning a simultaneous cognitive task.[12]

Movement monitors that assess whole-body joint kinematics, spatial and temporal gait characteristics, and balance during walking and climbing stairs are replacing non-portable systems of motion analysis.[6] Studies using wireless inertial sensors show that patients with multiple sclerosis who have minimal gait impairment can have abnormal postural sway[13] or dysfunction of the lower limbs.[14] Advantages of wireless systems include small size and weight and ability to collect, process, and rapidly analyse data from multiple sensors. The principal value of these tools is the ability to continuously monitor walking in a real-world environment to detect fluctuations during the day and trends over time. These measures capture different aspects of walking and mobility. Which aspect is most informative at different levels of disability in patients with multiple sclerosis or NMOSDs requires further study.

Neuropathic pain and bladder, bowel, and sexual dysfunction decrease quality of life and are common in patients with multiple sclerosis or NMOSDs with spinal cord involvement.[15–18] Permanent bladder or erectile dysfunction out of proportion to motor or sensory sequelae are particularly suggestive of involvement of the caudal spinal cord, which is characteristic of myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease.[19] The bowel–bladder Functional System Score of the EDSS captures patient self-reported bladder, bowel, and sexual dysfunction.[8] However, specialised testing is required for quantitative assessment.

Evoked potentials

Somatosensory evoked potentials detect damage involving the dorsal column of the spinal cord, and motor evoked potentials detect damage in the lateral column, although slowed conduction and loss of amplitude are pathologically non-specific.[20] Multimodal evoked potentials correlate with the EDSS both cross-sectionally and longitudinally[21] and predict disease progression over 3 years[21] and 20 years,[22] so they merit consideration as outcome measures in phase 2 clinical trials to assess the efficacy of neuroprotective and repair strategies.[23] The use of multimodal evoked potentials in multicentre trial studies of patients with multiple sclerosis requires standardisation of equipment and procedures within and between centres to reduce variability over time and shortening of the acquisition time. Absence of multimodal evoked potential responses in patients with advanced multiple sclerosis might preclude using somatosensory evoked potentials and motor evoked potentials of the lower extremities; assessment of the upper extremities might be informative in this situation.[20]

Asymptomatic abnormalities in evoked potentials are uncommon in patients with NMOSDs, and reduced or absent evoked responses are more common than decreased latency.[24] The severity of abnormalities of somatosensory and motor evoked potentials of the lower extremities correlate with the severity of relapses in patients with NMOSDs.[25] Further studies are needed to assess the ability of multimodal evoked potentials to distinguish optic neuritis or myelitis in NMOSDs from multiple sclerosis and their usefulness for monitoring NMOSDs over time in clinical practice and in clinical trials.

Biomarkers

AQP4 antibodies are sensitive and specific biomarkers which have greatly facilitated the diagnosis of NMOSDs and the definition of previously unrecognised clinical features, such as area postrema and diencephalic syndromes.[2] The diagnosis and characterisation of anti-MOG antibody disease is also evolving rapidly.[26] There is no comparable diagnostic biomarker for multiple sclerosis, a major unmet need. The presence of CSF-specific oligoclonal bands supports the diagnosis of multiple sclerosis and provides evidence against other diseases, including NMOSDs.[27] The 2017 revisions of the McDonald diagnostic criteria for multiple sclerosis[4] allow the presence of CSF-specific oligoclonal bands to substitute for demonstration of temporal dissemination in patients with a clinically isolated syndrome and dissemination in space shown clinically or by MRI.

The best validated non-imaging biomarker to monitor disease activity in patients with multiple sclerosis or NMOSDs is NfL concentration in CSF or blood.[7] Increasing NfL concentration reflects ongoing axonal damage irrespective of cause or anatomic location. In patients with multiple sclerosis, NfL concentration relates most closely to inflammatory lesion activity underlying acute relapses and, to a lesser extent, to the neurodegeneration underlying disease progression.[7] In a longitudinal observational study of 259 patients with multiple sclerosis,[28] baseline blood NfL concentration was positively associated with loss of spinal cord volume, relapse, and disability worsening over 2 and 5 years. Blood NfL also shows promise as a marker of treatment response; patients receiving disease-modifying therapy have lower concentrations of NfL than untreated patients, and concentrations decrease when patients switch from low-efficacy to high-efficacy therapy.[29,30]

NfL concentrations have been studied in patients with NMOSDs and in those with anti-MOG antibody disease. CSF NfL concentration is higher in patients with NMOSDs

	Lesion length and location on sagittal images	Location on axial images	T2 signal characteristics	T1 signal characteristics	Gadolinium enhancement
Multiple sclerosis[34,35]	Usually <1 vertebral segments; consistently <3 vertebral segments*	Multiple, asymmetrical	Hyperintense	Isointense or hypointense in chronic lesions studied with 3T MRI scanners, especially in patients with progressive multiple sclerosis	Present in most acute lesions; variable pattern: homogeneous, but ring-enhancing in about 20% of lesions
NMOSD (AQP4)[34,36-39]	About 85% of acute lesions span >3 vertebral segments;† chronic lesions can be short or replaced by long segments of atrophy or myelomalacia (pseudosyrinx)	Usually central; can be unilateral or even peripheral; can vary over the length of the lesion	Hyperintense and in about 90% of patients associated with extremely hyperintense lesions (bright spotty lesions)§	Usually hypointense in acute lesions	Present in almost all acute lesions; variable pattern, but ring-enhancing in about 30% of lesions
NMOSD (MOG)[40]	Acute myelitis spanning >3 vertebral segments; can occur in any part of the spinal cord, but in caudal spinal cord in about 75% of patients with NMOSD (MOG) *vs* 20% of patients with multiple sclerosis	Acute myelitis associated with single, but occasionally multiple, lesions	Hyperintense	Usually hypointense	Usually present but somewhat less frequent than in NMOSD (AQP4)
Infarction[41]	About 60% of lesions span >3 vertebral segments; can be normal when performed within first hours after symptom onset	Variable; about 65% of lesions associated with anterior grey matter specific lesions (owl eyes);‡ 30% of lesions with homogenous central grey or entire spinal cord cross-section	Hyperintense; about 40% of lesions have a linear, pencil-like configuration in anterior spinal cord	Commonly evolve into T1 hypointense lesions over months	In about 90% of lesions, there is linear enhancement on sagittal images corresponding to distribution of grey matter in the spinal cord
Viral myelitis[42]	Usually spanning >3 vertebral segments	Variable; can be associated with owl eye appearance (enterovirus) or central spinal cord (herpesvirus)	Hyperintense	Variable	Variable
Sarcoidosis[43]	Spanning >3 vertebral segments in most patients	Central or entire cross-sectional area	Hyperintense	Hypointense in about 50% of patients	Posterior subpial homogeneous enhancement over long segments of the spinal cord; central canal enhancement common; trident sign on axial images; ring enhancement not seen
Spondylotic compressive myelopathy[44]	Variable; can span >3 vertebral segments	Central	Hyperintense	May have disc-like pattern corresponding to site of enhancement	Disc-like (flat pancake) pattern of enhancement at point of maximum spinal cord impingement often present
Paraneoplastic myelopathy[45]	Usually over multiple vertebral segments	Symmetrical, tract-specific lesion	Hyperintense	Isointense	Variable; homogeneous gadolinium enhancement in approximately 50% of patients

NMOSD=neuromyelitis optica spectrum disorder. AQP4=aquaporin-4. MOG=myelin oligodendrocyte glycoprotein. *Chronic multiple sclerosis lesions can appear confluent on sagittal images, causing radiological diagnostic confusion with other conditions, such as neuromyelitis optica, associated with longitudinally extensive lesions; axial images usually clarify confusions by revealing central and peripheral conglomerated lesions in patients with multiple sclerosis. †In patients not receiving immunosuppression. ‡Reported to occur with equal frequency in patients with acute myelitis associated with NMOSD.[46] §Can also occur in about 30% of patients with spinal cord infarcts.

Table: **MRI characteristics of spinal cord lesions in immune-mediated, vascular, and compressive myelopathies**

than in those with multiple sclerosis or other neurological diseases,[31] reflecting the more severe and acute tissue damage seen in NMOSDs. Blood NfL concentration also relates to the frequency and severity of relapses in patients with NMOSDs.[32]

Radiological assessment of spinal cord lesions

Diagnosis and differential diagnosis

Multiple sclerosis, NMOSDs, and acute disseminated encephalomyelitis can cause acute myelitis, generally worsening over days to weeks and followed by stabilisation or recovery.[4] Clinical deterioration that continues beyond 3 weeks, particularly over months, suggests another aetiology, such as sarcoidosis, dural arteriovenous fistula, spinal cord tumour, or a metabolic or paraneoplastic disorder.[33] The differential diagnosis between these disorders is aided by differences in imaging findings (table).

The spinal cord is one of four anatomical locations incorporated into the 2017 McDonald diagnostic criteria for multiple sclerosis to document dissemination in space in patients who present with a clinically isolated syndrome suggestive of multiple sclerosis.[4] New or gadolinium-enhancing spinal cord lesions can be used to document dissemination in time.[4] Multiple sclerosis lesions of the spinal cord are typically wedge-shaped in axial images, ovoid in sagittal images, and usually less than one vertebral segment in length and rarely over three segments (figure 1). Lesions are most commonly located in the periphery of the spinal cord (mainly posteriorly and

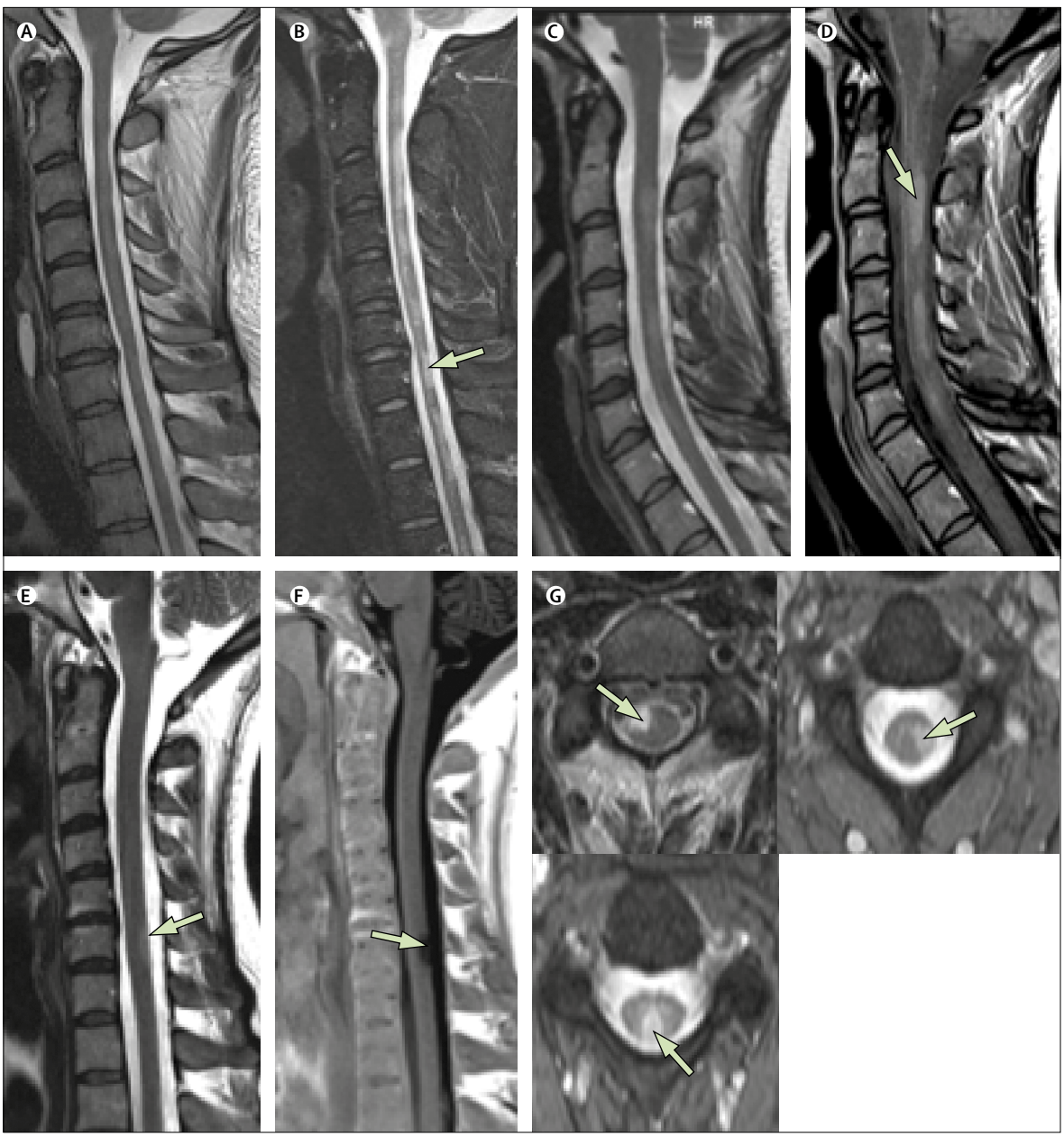

Figure 1: **Potential diagnostic protocols for spinal cord imaging in patients with multiple sclerosis**
Three potential protocols for use in the clinical setting are shown. Each protocol consists of two sagittal images: T2 sagittal image (A) and short tau inversion recovery sagittal image (B); T2 sagittal image (C) and proton density sagittal image (D); or T2 sagittal image (E) and phase-sensitive inversion recovery sagittal image (F). If lesions are seen on sagittal scans, axial scans should be acquired. T2-weighted axial images are shown in (G). The arrows indicate typical lesions in patients with multiple sclerosis. Similar imaging protocols can be used in the diagnosis of patients with neuromyelitis optica spectrum disorders.

laterally) but can also involve the central grey matter. Spinal cord lesions are particularly helpful for differential diagnosis because they do not occur in most common neurological conditions, such as migraine and cerebrovascular disorders, which can also be associated with multifocal T2 hyperintensities in the cerebral white matter and are sometimes misdiagnosed as multiple sclerosis.[47] Detection of multiple peripheral asymmetric lesions in the spinal cord is almost pathognomonic of multiple sclerosis. Occasionally, in patients with progressive multiple sclerosis, the presence of diffuse spinal cord lesions that mimic a longitudinally extensive lesion of the spinal cord leads to diagnostic uncertainty.[48] However, high-resolution axial MRI usually demonstrates that the apparently confluent lesion comprises multiple discrete lesions.

Different from multiple sclerosis, NMOSDs and acute disseminated encephalomyelitis produce longitudinally

extensive lesions of the spinal cord, which can be similar in appearance.[49] MOG antibody-associated disease can also present with longitudinally extensive spinal cord lesions, which occur in the caudal spinal cord more often than in AQP4 antibody-associated disease.[19] Lesions in NMOSDs typically involve the central spinal cord and can initially have a linear appearance which later becomes longitudinally extensive.[50] So-called bright spotty objects (persistent areas of marked T2 hyperintensity within lesions which can have similar or higher intensity than CSF on T2-weighted images, but not as low intensity as CSF on T1-weighted images) are characteristic spinal cord lesions in patients with NMOSDs.[37] Acute spinal cord lesions in patients with NMOSDs are hypointense on T1 images, but this appearance is rare in patients with multiple sclerosis when using a T1 spin echo sequence. Chronic lesions in patients with NMOSDs, multiple sclerosis, and other conditions, including spinal cord infarction, can be hypointense on T1 images.[35]

Diagnostic criteria have used lesion extension over more than three contiguous vertebral segments to indicate NMOSDs.[2] However, in patients with NMOSDs developing acute myelitis while not on treatment, approximately 15% have lesions shorter than three vertebral segments, which can lead to a misdiagnosis of multiple sclerosis (figure 2).[51] In those patients, the diagnosis should be based on clinical, demographic, and serological features. Conversely, longitudinally extensive lesions of the spinal cord have been reported in up to 10% of paediatric patients with multiple sclerosis,[52] though it is possible, in retrospect, that some children had MOG antibody-associated disease.[19] Chronic lesions in patients with NMOSDs can be nonspecific in appearance and shorter than three vertebral segments.[53]

Acute lesions in patients with NMOSDs almost always demonstrate gadolinium enhancement, most often patchy, irregular, and prominent in the lesion margin. Although ring enhancement can be seen in spinal cord lesions in both patients with multiple sclerosis and NMOSDs,[34] it distinguishes NMOSDs from other aetiologies of longitudinally extensive myelopathy (table, figure 3).[33] In particular, ring enhancement is rarely encountered in patients with sarcoidosis, spondylotic myelopathy, dural arteriovenous fistula, spinal cord infarction, or paraneoplastic myelopathy.[34] Linear dorsal subpial enhancement over two vertebral segments is characteristic of sarcoidosis, although it can also occur in patients with vitamin B12 deficiency.[54]

In summary, no single radiological finding or a combination thereof is pathognomonic of a specific aetiology. Synthesis of clinical and radiological factors and testing for AQP4 and MOG autoantibodies can yield a specific diagnosis in many patients who would have been previously classified as having idiopathic transverse myelitis.[55]

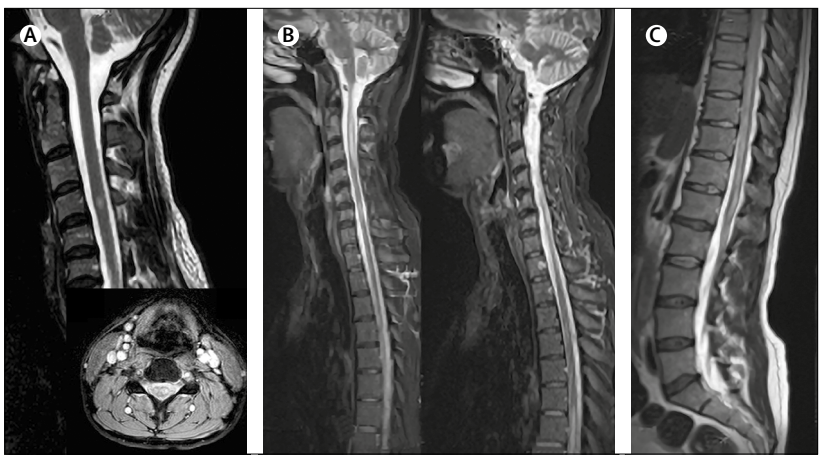

Figure 2: **Short spinal cord lesions in a patient with neuromyelitis optica spectrum disorder**
A 39-year-old male patient presented with imbalance and gait impairment. Spinal cord MRI obtained at the time of presentation showed a short lesion in the central spinal cord at the C5 level (A). Brain MRI showed lesions suggestive of inflammatory demyelination (not shown). Lumbar puncture demonstrated CSF-specific oligoclonal bands. In his medical history, there were two possible episodes of optic neuritis and weakness in his legs occurring about 10 years earlier, when he was living abroad. He was diagnosed with relapsing-remitting multiple sclerosis and treated first with interferon beta. Because of recurrent episodes of partial myelitis over the subsequent 5 years, treatment was changed to fingolimod. Over the following year and after starting fingolimod treatment, he experienced two further partial myelitis episodes. While off fingolimod, in preparation for monoclonal antibody therapy, he presented with weakness and numbness of all four limbs and urinary retention. Another spinal cord MRI during the episode of myelitis showed a longitudinally extensive lesion typical of neuromyelitis optica spectrum disorder (B and C), leading to a change in diagnosis to neuromyelitis optica spectrum disorder.

MRI to detect asymptomatic spinal cord lesions

Brain MRI is useful to detect subclinical disease activity in patients with multiple sclerosis;[56] the role of MRI to screen for asymptomatic lesions of the spinal cord in patients with multiple sclerosis and NMOSDs is less clear. Asymptomatic spinal cord lesions are common in patients with CNS demyelinating diseases, including in about 35% of patients with radiologically isolated syndrome,[57] 27–53% of patients with non-spinal clinically isolated syndrome,[58] and 83% of patients with early relapsing-remitting multiple sclerosis.[59] In patients with radiologically isolated syndrome, asymptomatic lesions of the spinal cord are associated with increased risk of becoming symptomatic, particularly with a progressive course. In a longitudinal study of 453 patients with radiologically isolated syndrome,[57] 128 (28%) developed symptomatic multiple sclerosis during follow-up. Among those 128 patients, 15 (100%) of 15 who developed progressive symptoms from onset (ie, primary progressive multiple sclerosis) had spinal cord lesions at first detection versus 72 (64%) of 113 patients whose first clinical manifestation was an attack. In patients with non-spinal clinically isolated syndrome, the number of asymptomatic spinal cord lesions predicts the risk of a second clinical event,[60] and disability at 2-year[60] and 5-year follow-up.[61] Thus, spinal cord MRI is advisable in the evaluation of patients with clinically isolated syndrome.

In a longitudinal study[62] of 103 patients with relapsing-remitting multiple sclerosis with median follow-up of 17 months, asymptomatic lesions of the spinal cord were

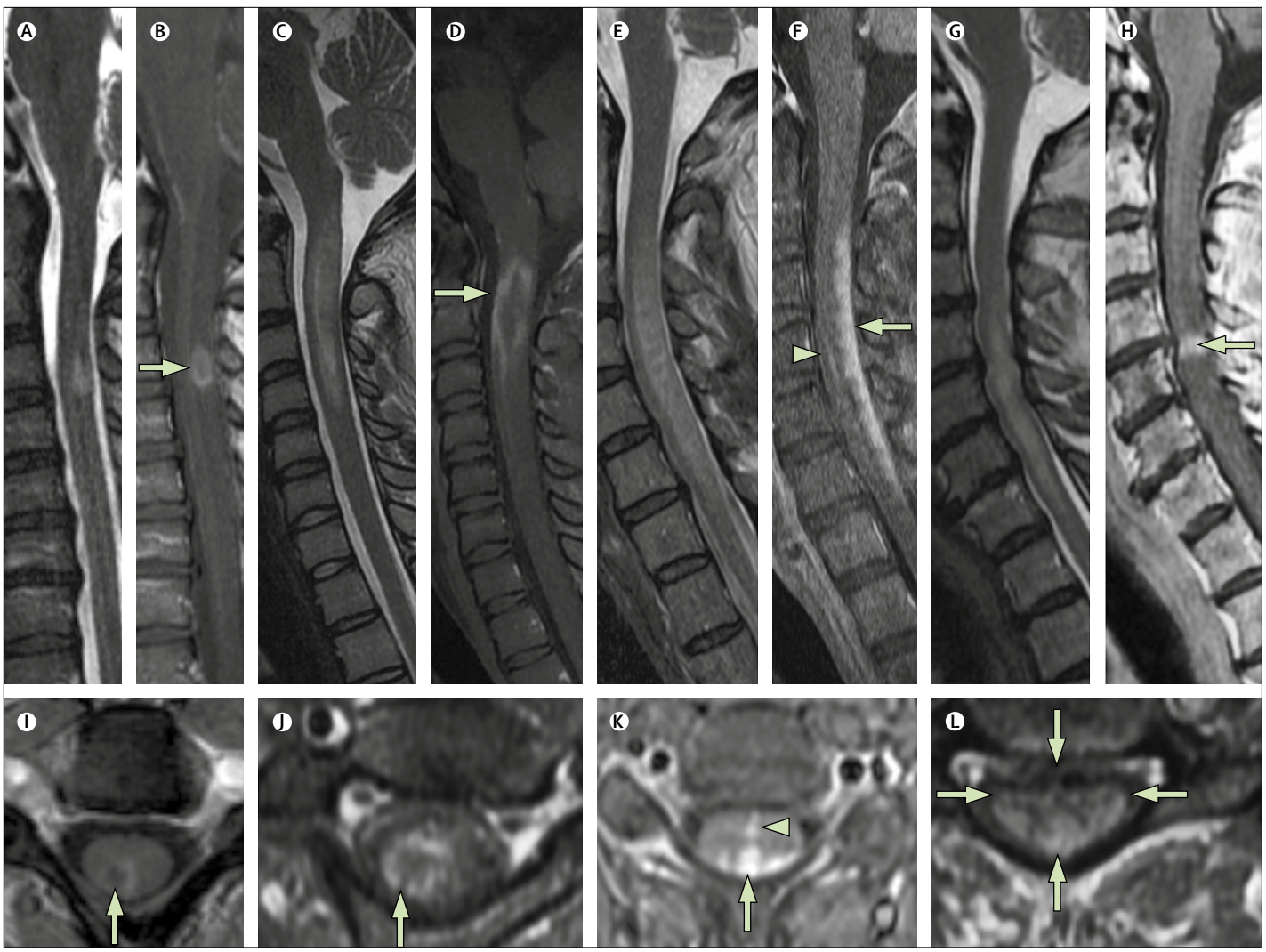

Figure 3: **Gadolinium enhancement patterns in myelopathy aetiologies**
Multiple sclerosis: short T2 hyperintense lesion on sagittal MRI extending one vertebral segment (A) has accompanying ring enhancement on T1 post-gadolinium sagittal (B, arrow) and axial (I, arrow) sequences. AQP4 antibody-associated neuromyelitis optica spectrum disorder: a longitudinally extensive T2 hyperintense lesion on sagittal images (C) demonstrates ring enhancement on T1 post-gadolinium sagittal (D, arrow) and axial (J, arrow) sequences. Sarcoidosis: a longitudinally extensive T2 hyperintense lesion on sagittal images (E) has accompanying enhancement on T1 post-gadolinium sequences that extends linearly along the dorsal subpial surface (F and K, arrow), with enhancement of the central canal (F and K, arrowhead), also evident on axial sequences where it forms a trident-like pattern (K). Cervical spondylosis: a longitudinally extensive T2 hyperintense lesion on sagittal sequence (G) has accompanying enhancement on T1 post-gadolinium sequences which forms a transverse band (pancake-like) just underneath the site of maximal stenosis (H, arrow) and involves the white matter of the spinal cord only on axial sequences (L, arrows). AQP4=aquaporin-4.

detected in 26 (25%) patients compared with 45 (44%) patients who had an asymptomatic brain lesion during follow-up. Only ten (10%) of 103 patients developed asymptomatic lesions in the spinal cord but not the brain during follow-up. Thus, spinal cord MRI might be less useful than brain MRI for routine clinical monitoring of patients with relapsing-remitting multiple sclerosis.

Asymptomatic spinal cord lesions occur in patients with NMOSDs but are less common than in those with multiple sclerosis, and their ability to predict future disease activity and disability is unclear.[63] Additional longitudinal studies are needed in patients with multiple sclerosis and NMOSDs to clarify the incidence of new asymptomatic lesions in the spinal cord compared with the brain, their impact on disease course, and their implications for disease therapy.

Technical aspects of clinical imaging

Spinal cord MRI is less used than brain MRI to monitor status of multiple sclerosis in clinical practice; it prolongs the imaging session and, as a result, elevates cost. Because spinal cord MRI is often adversely affected by several artefacts generated by susceptibility differences at tissue interfaces, CSF pulsation, respiratory motion, and swallowing, it is technically challenging to obtain good quality images. Methods to mitigate such artefacts (eg, cardiac gating, use of pre-saturation slabs, fast imaging sequences, and tailored phase-array coils) have been developed.[64]

A protocol that images the whole spine is generally preferred. However, because MRI detects lesions of the spinal cord in patients with multiple sclerosis most often in the cervical region,[65] a single sagittal acquisition from cervical level 1 to the upper thoracic spinal cord might be adequate and would improve image resolution because of the smaller field of view compared with whole spinal cord coverage. The preferred protocol to detect focal lesions includes a combination of two sagittal sequences, either both T2-weighted sequences, such as fast spin echo and short tau inversion recovery, which allows fat suppression, or a T2-weighted and a proton density-weighted sequence. Alternatively, a fast spin echo T2-weighted or a short tau inversion recovery sequence can be combined with a T1-weighted sequence designed to enhance the contrast between tissues with different T1 relaxation times, such as phase-sensitive inversion recovery, which nulls the signal of normal white matter (figure 1). The combination of T2-weighted sequences with short tau inversion recovery or phase-sensitive inversion recovery sequences could offer the greatest contrast between lesions and surrounding tissue and the highest sensitivity and specificity for detecting lesions in the cervical spinal cord.[66]

Lesions detected in sagittal images ideally should be confirmed by acquisition of axial images (figure 1). Axial imaging covering the whole spinal cord can be acquired in an acceptable length of time with parallel imaging acceleration and it detects more lesions than sagittal imaging,[65] especially small lesions in the spinal cord periphery.[67] In some cases, the acquisition of axial slices of the entire spinal cord over 5 minutes with slice thickness of 6 mm allows rejection of the equivocal abnormalities seen on sagittal images.[65] If two sagittal sequences are not acquired, a biplanar protocol (T2-weighted sagittal and axial slices of the entire spinal cord) can be considered.

Follow-up scans do not routinely require gadolinium administration, especially if no lesions are detected. Gadolinium is retained in the brain, although no harmful effects of deposition in the CNS have been reported yet.[68] If lesions are seen, then gadolinium-enhanced (single dose, 0·1 mmol/kg bodyweight, minimum delay time 5 min) T1-weighted spin echo sequences are advised[69] to assess dissemination in time for the diagnosis of multiple sclerosis.[4] Conversely, an enhancement pattern atypical of multiple sclerosis might indicate an alternative diagnosis.

Advanced MRI techniques

Technical improvements in MRI acquisition and analysis have made advanced spinal cord imaging more feasible. The most promising techniques to study the spinal cord are myelin water imaging, magnetisation transfer imaging, diffusion tensor imaging, and magnetic resonance spectroscopy. At present, however, advanced spinal cord imaging is mostly restricted to research studies at individual sites. Additional research is needed to incorporate these studies into multicentre studies, including clinical trials. Translation to a clinical setting is likely to be restricted to selected clinical cases at sites with experience with the imaging techniques.

Myelin water imaging provides more pathological specificity for demyelination than standard MRI. Although myelin content decreases in the normal-appearing white matter in patients with multiple sclerosis, such a decrease is restricted to lesions in patients with NMOSDs.[70] Magnetisation transfer imaging is less pathologically specific than myelin water imaging because it reflects demyelination, axonal loss, and cellular tissue changes, but is more sensitive. The acquisition sequence is readily available, and the data are relatively straightforward to analyse. The magnetisation transfer ratio demonstrates abnormalities related to multiple sclerosis in the spinal cord that cannot be detected by standard MRI and better explains clinical heterogeneity and severity of disability.[71]

Diffusion-weighted imaging methods, such as diffusion tensor imaging, also provide quantitative parameters that are pathologically specific and correlate with clinical disability.[72] Parameters derived from diffusion tensor imaging in lesions and normal-appearing spinal cord differ between multiple sclerosis and NMOSDs, reflecting the more severe acute tissue damage the latter causes.[73] Further work is needed to overcome technical challenges to acquire standardised, high-quality data across scanner manufacturers and sites. Advanced diffusion MRI acquisition and modelling methods, such as q-space imaging[74] or neurite orientation dispersion and density imaging,[75] could provide more accurate information on spinal cord microstructure than diffusion tensor imaging.

Magnetic resonance spectroscopy measures the metabolite composition of tissues. The concentration of N-acetyl-aspartate is reduced in the lesions of patients with acute multiple sclerosis when compared with healthy controls, indicating neuronal loss or neuronal dysfunction which partially recovers in some lesions over time.[76] Lower myoinositol and creatine values are detected in lesions of patients with NMOSDs when compared with healthy controls and patients with multiple sclerosis,[77] suggesting astrocytic damage. An in-vivo study at 3T with post-mortem validation extended the metabolic profile of normal spinal cord to include neurotransmitters and antioxidants.[78] Application of this new technique to spinal cord disease is needed.

Advanced MRI imaging has been used to study the association between focal damage of the spinal cord and sensory–motor impairment in patients with multiple sclerosis measured by column-specific outcomes. CSF-normalised magnetisation transfer signal of the dorsal column correlates with vibration sensation, and the lateral column signal correlates with ankle strength.[79] Diffusion MRI measurements in the dorsal column correlate with vibration sensation, whereas diffusion measurements in dorsal and lateral columns correlate

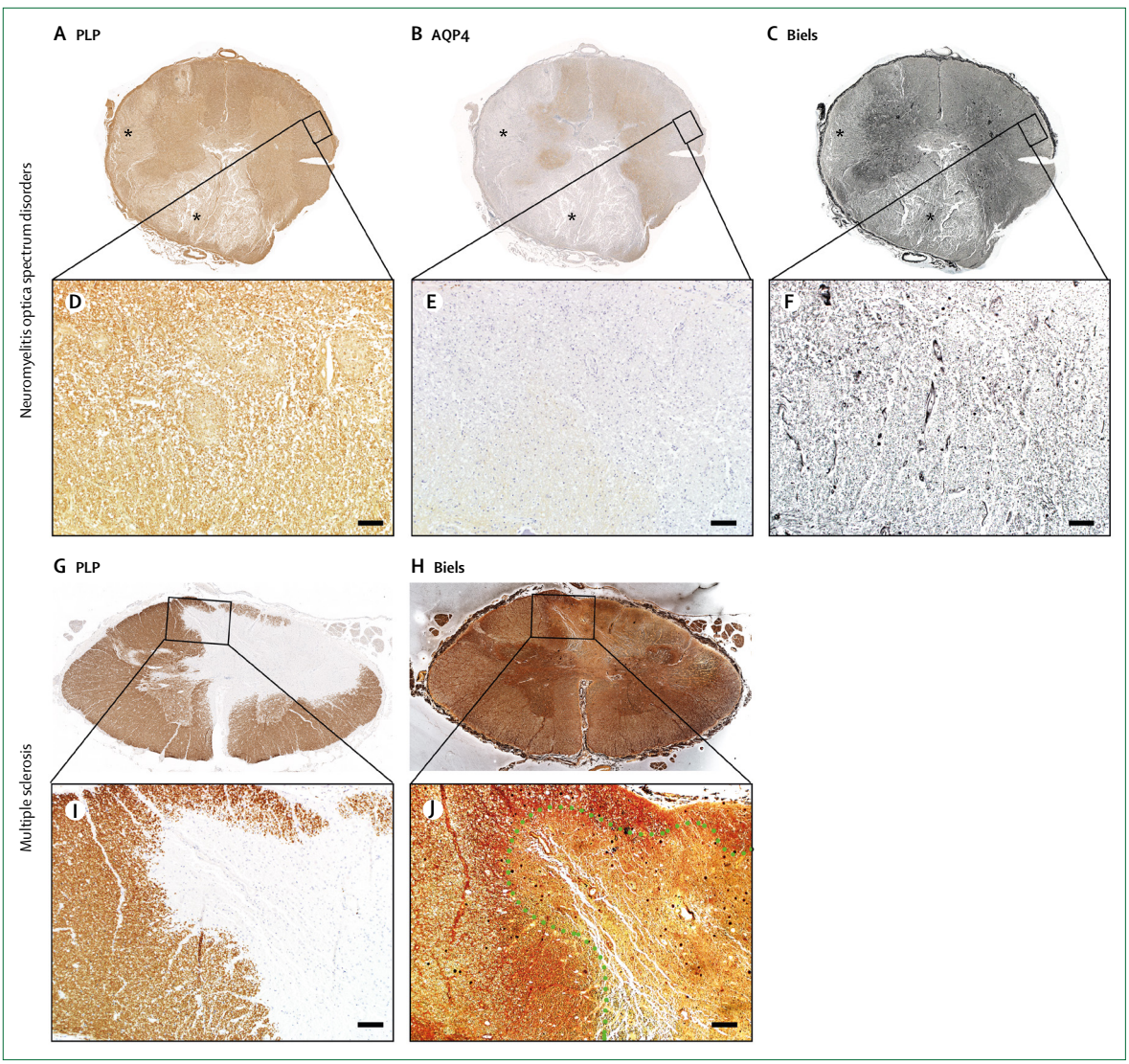

Figure 4: **Myelin and axonal pathology in patients with multiple sclerosis or neuromyelitis optica spectrum disorders**
Neuromyelitis optica spectrum disorders: myelin PLP immunohistochemical staining of the spinal cord shows demyelinating lesions (A, asterisk) with AQP4 loss on immunohistochemical staining (B, asterisk) and axonal loss with Bielschowsky silver staining (C, asterisk). An early pre-demyelinating lesion is characterised by myelin preservation (boxed area in A and D), AQP4 loss (boxed area in B and E), and axonal preservation (boxed area in C and F). Multiple sclerosis: PLP immunohistochemical staining shows a chronic demyelinating lesion in the spinal cord in MS (G and I); Bielschowsky silver staining shows axonal damage characterised by a reduction in axons (H and J, the green dotted line highlights the lesion border). Scale bars=100 μm. AQP4=aquaporin-4. PLP=proteolipid protein.

with the Timed 25-Foot Walk and 9-Hole Peg tests.[80] A cross-sectional study at 3T in 21 patients with early primary progressive multiple sclerosis and 24 healthy controls matched for age and sex showed an association between parameters of column-specific quantitative imaging and postural stability and vibration sensation.[74] These studies demonstrated that advanced spinal cord imaging detects clinically relevant in-vivo changes potentially applicable to the diagnosis and monitoring of multiple sclerosis. These approaches might not be as applicable to patients with NMOSDs, whose lesions are larger and less tract-specific than in patients with multiple sclerosis.

MRI-assessed spinal cord atrophy as a clinical trial endpoint

Quantification of spinal cord atrophy (measuring progressive reduction in the cross-sectional spinal cord area over time) is the most attractive advanced technique for clinical applications because of its association with disability in multiple sclerosis and NMOSDs.[3] In patients with multiple sclerosis, spinal cord atrophy correlates with concurrent disability and predicts long-term outcome.[81] The rate of atrophy is faster in the spinal cord than in the brain and in patients with secondary progressive multiple sclerosis (2·2% per year) than in patients with clinically isolated syndrome who have no disease activity during

follow-up or who have early mild relapsing-remitting multiple sclerosis (0·5% per year).[61,81] Although patients with relapsing-remitting multiple sclerosis have more brain atrophy than spinal cord atrophy (especially in grey matter), patients with NMOSDs have more atrophy in the spinal cord than the brain,[82] suggesting different pathogenic mechanisms. Spinal cord atrophy can occur in patients with NMOSDs without spinal cord lesions,[83] suggesting the presence of subtle spinal cord pathology not visible on MRI or of diffuse brain atrophy leading to spinal cord atrophy. In patients with NMOSDs, the relation of spinal cord atrophy with disease activity and disability accrual is unknown.

Atrophy is unique among spinal cord imaging measures in that it has been used as a secondary outcome in clinical trials of progressive multiple sclerosis (appendix). However, trials have not shown a significant treatment benefit on this metric, which could be because of inefficacy of the intervention, enrolment of a non-informative study population, or variability in the measurement techniques available at the time. These limitations could be reduced by modifying eligibility criteria and by conducting trials in a single centre or only a few centres to permit better control on the technical aspects of imaging. An informative sample size was enrolled in a single-centre phase 2 trial of progressive multiple sclerosis by requiring recent onset of progressive disease, mild-to-moderate disability, documentation of progression in the previous 1 or 2 years, and modest spinal cord atrophy.[84] Although these restrictive eligibility criteria can improve the sensitivity of spinal cord atrophy as an outcome measure, they introduce recruitment challenges.

Spinal cord atrophy can be assessed with a 3D T1-weighted sequence (with isotropic resolution ≤1 mm³ to reduce the partial volume effect). Measurement of cross-sectional area of the upper cervical spinal cord is needed until automatic registration-based methods are available. Automated imaging techniques using registration of scans over time will increase the precision of measurements of spinal cord atrophy, making detection of treatment effects more feasible. Acquisition of 3D T1 volumetric brain scans to quantify both brain and upper spinal cord atrophy[85] might, in the meantime, remove the need for additional imaging of the spinal cord and facilitate incorporation of spinal cord atrophy in clinical trials.

Spinal cord atrophy could be clinically relevant and sensitive for monitoring patients with progressive multiple sclerosis and could be considered as a primary endpoint in phase 2 trials with careful consideration of the study population and methodological issues related to imaging. The role of spinal cord atrophy as an outcome in clinical trials of patients with NMOSDs is unclear. The frequency and severity of relapses remain the recommended endpoints for clinical trials of patients with NMOSDs.[86]

***Panel*: Directions for future research**

- Further study of differences in the pathophysiology of multiple sclerosis and neuromyelitis optica spectrum disorders to clarify the pathobiology of axonal loss and accrual of disability
- Development and validation of better tools for assessment of gait and mobility, activity monitors, and other paraclinical tools to detect and track spinal cord involvement
- Standardisation and multicentre applicability of electrophysiology tools that assess spinal cord function longitudinally
- Incorporation of available clinical and imaging spinal cord assessments into routine monitoring of patients and into outcomes used to evaluate novel therapies
- Incorporation of recognised imaging patterns and especially patterns of gadolinium enhancement to facilitate differential diagnosis of inflammatory myelopathies and distinguish inflammation from spinal cord compression and infarction; assessment of these patterns in clinical practice
- Development of automated techniques for image registration to increase precision and reduce variability of longitudinal (over time) quantification of spinal cord atrophy

Pathophysiology of disability accrual

Disability accrues in patients with multiple sclerosis predominantly from disease progression (gradual worsening distinct from relapses).[87] By contrast, although severe and permanent spinal cord-related disability is common in patients with NMOSDs, gradual progression of disability is rare.[88] Pathological differences between multiple sclerosis and NMOSDs could explain this difference in clinical course.

Factors that lead to progression in multiple sclerosis include acute inflammatory axonal injury and degeneration of chronically demyelinated axons in focal lesions and in white and grey matter that appears normal on standard MRI.[89] Progressive worsening of disability associated with a single demyelinating lesion of the spinal cord (solitary sclerosis) illustrates that neurodegeneration in a single focal lesion can be sufficient to cause progressive motor impairment.[90] The long axons in ascending and descending pathways of the spinal cord are particularly susceptible to axonal transection in acute inflammatory lesions and to degeneration in chronically demyelinated lesions (figure 4).

The pathological mechanisms damaging the spinal cord in patients with multiple sclerosis overlap with those in the brain, but with several differences. Cortical demyelination in the brain, usually not detectable with MRI, is strongly associated with disability and in some studies has been related to inflammatory cell infiltrates of the meninges.[91] Iron accumulation has been associated with

Search strategy and selection criteria

In preparation of this Review, the authors conducted literature searches in PubMed (publications originally in or translated into English from Jan 1, 1980, to Oct 15, 2018, with a focus on papers since 2010 but including earlier publications as appropriate) using the search terms: "multiple sclerosis", "neuromyelitis optica spectrum disorder", and "spinal cord disease", and the combination of these disease descriptors with "clinical signs and symptoms", "assessment", "outcomes", "imaging", "electrophysiology", "biomarker", and "activity monitor".

neurodegeneration, possibly through generation of reactive oxygen radicals.[92] Mitochondrial dysfunction and impaired transport reduce energy production and amplify the effects of reactive oxygen intermediates.[93] Lesions are particularly common in perfusion watershed areas of the brain (ie, white matter at the intersection of perfusion territories supplied by the anterior, middle, and posterior cerebral arteries), suggesting that ischaemia contributes to demyelination and neurodegeneration.[94] As in the brain, demyelination and neurodegeneration in the spinal cord are present in radiographically normal-appearing white matter and grey matter[95] and might be associated with meningeal inflammation.[96] However, the spinal cord appears relatively spared from the effects of ischaemia and iron accumulation.[97]

The apparent absence of gradual progression in patients with NMOSDs could be an observational artefact, if major disability from attacks obscures further worsening. More probable explanations for this observation are the severe acute axonal destruction in NMOSDs lesions, the scarcity of viable chronically demyelinated axons (figure 4), and the absence of lesions in the grey matter of the cerebral cortex.[98] Evidence of subclinical brain or spinal cord injury in patients with NMOSDs is controversial.[99] Diffuse white matter injury and atrophy of the cervical spinal cord have been reported in patients with NMOSDs without a history of myelitis.[83] By contrast, thinning of the retinal nerve fibre layer detected by optical coherence tomography is rare in patients with NMOSDs without a history of optic neuritis.[100]

Thus, several quantitatively different mechanisms lead to differences in clinical course and pattern of permanent disability accrual in patients with multiple sclerosis and NMOSDs. Although the exact mechanisms are uncertain, degeneration of chronically demyelinated but initially viable axons, especially in the spinal cord, appears to be the major cause of gradually worsening disability in patients with progressive multiple sclerosis.[89] By contrast, degeneration of acutely injured axons in patients with NMOSDs appears to be the principal mechanism of disability in this disorder, but progressive disability worsening is uncommon.

Conclusions and future directions

Spinal cord involvement causes much of the disability reported in patients with multiple sclerosis and NMOSDs but the mechanisms underlying disability accrual probably differ.[87,88] Whereas degeneration of chronically demyelinated axons might explain the progression of disability in patients with multiple sclerosis,[89] the scarcity of cortical lesions and the presence of demyelinated but viable axons account for the absence of progression in patients with NMOSDs.[98] The pathogenesis of the formation of spinal cord lesions and its relation to accrual of permanent disability in both disorders requires further study (panel) to understand the origin and evolution of outcomes related to the spinal cord, and to better define the role of spinal cord assessment in diagnosis and disease monitoring.

More sensitive and better standardised methods to assess clinical manifestations related to the spinal cord over time are needed to monitor the course of disease and the response to therapy. Comprehensive quantitative assessment of gait and mobility is sensitive to subtle impairment[5] but is currently not routinely performed. It needs further validation to be useful for longitudinal monitoring, both in clinical practice and multicentre therapeutic trials of patients with multiple sclerosis and NMOSDs. Electrophysiological approaches can detect and quantify subclinical pathology of the spinal cord[20] but need better standardisation and reproducibility for routine application to multicentre studies.

The time over which clinical manifestations evolve,[4] the associated imaging characteristics (especially gadolinium enhancement pattern),[49] and biomarkers (eg, AQP4 and MOG autoantibodies)[2,26] help to distinguish myelopathy from multiple sclerosis, NMOSDs, and other disorders. However, because clinical and radiological features sometimes overlap, future studies to identify novel imaging biomarkers to differentiate disorders are still needed. Application of best practices for MRI acquisition of the spinal cord improves image quality.[64] Spinal cord MRI helps to predict prognosis in patients with multiple sclerosis.[60,61] Whether it is useful for assessing prognosis in patients with NMOSDs and monitoring for subclinical activity in either disorder is less clear.[62,63] Advanced spinal cord imaging techniques might improve pathological specificity.[70,79,80] However, their implementation presents several technical challenges currently restricting them to the research setting. Spinal cord atrophy is attractive as a measure of overall spinal cord damage in patients with multiple sclerosis and NMOSDs, and has already been used as an endpoint in several clinical trials of multiple sclerosis (appendix), though with variable success. It might become more useful once optimised to the level of reproducibility of brain atrophy measurements.[85]

Overall, there is a need to improve and validate clinical, electrophysiological, biomarker, and imaging measures of spinal cord involvement in multiple sclerosis and NMOSDs, especially across centres, to increase translation

of spinal cord assessment into patient care and clinical trials. These knowledge gaps signal the need for close cooperation between investigators with wide-ranging areas of expertise.

Contributors

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Declaration of interests

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