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Understanding the Pathophysiology and Magnetic Resonance Imaging of Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders

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Magnetic resonance imaging (MRI) has been extensively applied in the study of multiple sclerosis (MS), substantially contributing to diagnosis, differential diagnosis, and disease monitoring. MRI studies have significantly contributed to the understanding of MS through the characterization of typical radiological features and their clinical or prognostic implications using conventional MRI pulse sequences and further with the application of advanced imaging techniques sensitive to microstructural damage. Interpretation of results has often been validated by MRI-pathology studies. However, the application of MRI techniques in the study of neuromyelitis optica spectrum disorders (NMOSD) remains an emerging field, and MRI studies have focused on radiological correlates of NMOSD and its pathophysiology to aid in diagnosis, improve monitoring, and identify relevant prognostic factors. In this review, we discuss the main contributions of MRI to the understanding of MS and NMOSD, focusing on the most novel discoveries to clarify differences in the pathophysiology of focal inflammation initiation and perpetuation, involvement of normal-appearing tissue, potential entry routes of pathogenic elements into the CNS, and existence of primary or secondary mechanisms of neurodegeneration.

Keywords: MRI; Neuromyelitis optica spectrum disorders; Multiple sclerosis; Pathophysiology

INTRODUCTION

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are autoimmune conditions affecting the central nervous system (CNS) [1,2]. For decades, these diseases have been considered part of the same spectrum, with NMOSD classified as an aggressive variant of MS. The reason for this is the partial overlap of their clinical manifestations, which in both cases include inflammatory involvement of the optic nerve and spinal cord, in the form of acute optic neuritis and transverse myelitis. However, these manifestations are more severe in patients with NMOSD. Optic neuritis in NMOSD is often bilateral and long (i.e., involving at least 50% of the optic nerve length) [2], and is associated with incomplete recovery [3] and potential blindness [4]. Similarly, acute myelitis is usually longitudinally extensive (i.e., involving at least three consecutive vertebral segments) [2] and patients almost invariably suffer from residual disabilities [3,4]. The severity of acute inflammatory activity in NMOSD leads to multistep disability accrual, in which residual disability is gained after attacks [4].

In contrast, recovery from acute episodes is usually good in patients with MS, but approximately 85% eventually develop secondary disability progression, in which motor worsening occurs irrespective of inflammatory episodes [5]. Table 1 summarizes the main clinical differences and

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Table 1. Main clinical and laboratory features of MS and NMOSD

Variables	MS	NMOSD
Age at onset, yr	20–40	30–50
Female/male ratio	2–3/1	4–9/1
Secondary progression	Common	Rare
CSF features		
Oligoclonal bands	Common	Rare
Pleocytosis	Mild	Moderate-Severe
High proteins	Rare	Common
Clinical manifestations	Heterogeneous (optic neuritis, transverse myelitis, hemispheric, brainstem)	Mainly optic neuritis, transverse myelitis, and area postrema syndrome
Optic neuritis		
Bilateral	Rare	Common
Recovery	Usually good	Partial
Transverse myelitis		
Longitudinally extensive	Rare	Common
Recovery	Usually good	Partial

MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, CSF = cerebrospinal fluid

similarities between patients with MS and NMOSD.

These clinical differences can be explained by the novel discovery of an antibody in the serum of patients with NMOSD that is not present in patients with MS or other neurological diseases [6]. This antibody targets aquaporin-4 (AQP4), a water channel protein highly expressed on astrocyte endfeet in the blood-brain barrier [7]. It belongs to the immunoglobin G1 (IgG1) subclass and can activate the complement cascade, leading to astrocyte death and secondary oligodendrocyte damage with demyelination [8].

This pathophysiological cascade differs from that of MS, a cell-mediated disorder in which autoreactive T cells promote primary damage to myelin, assisted by antigen-presenting cells (B cells, macrophages, dendritic cells, and microglia) through mechanisms that are still poorly understood [5].

Clinical Contribution of MRI

Most recommendations on the optimal magnetic resonance imaging (MRI) protocol for the clinical management of CNS autoimmune disorders come from the experience with MS, where MRI provides a substantial contribution to both diagnosis and treatment monitoring. Indeed, in clinical practice (as well as in research), MRI protocols are affected by high inter-center variability, which can limit the interpretation of results (i.e., differences in sequences acquired) and affect the standard of care. Therefore, international recommendations have been updated over the years to provide guidelines and standardized protocols for optimal diagnostic framing of MS and treatment monitoring [9,10]. At the time of diagnosis, emphasis is placed on the comprehensive acquisition of brain images, which must include contrast administration [9,10]. Although not recommended in the past, the latest guidelines highlight the importance of studying the spinal cord at initial evaluation [10]. However, longitudinal evaluation is currently not recommended, unless the patient is symptomatic for myelitis [10]. Advanced MRI sequences are usually considered optional, although atrophy measurement is becoming increasingly popular in MS, given its prognostic implications and the growing availability of automated software for its quantification [10]. However, it is worth mentioning that the application of these tools, especially in a longitudinal setting, should rely on the acquisition of three-dimensional (3D) images (better if isotropic) with multiple contrasts and should always be accompanied by the segmentation of lesions (because they can influence atrophy measurement). Centers should test these tools on a standard test dataset [11].

No specific recommendations are currently available for NMOSD; however, it is reasonable to assume that most principles applied to MS can also be translated to this disease. However, a body of evidence suggests that routine MRI acquisition for monitoring patients with asymptomatic NMOSD may not be recommended because asymptomatic lesion development is rare [12]. Our proposed optimal MRI protocol for the clinical management of MS and NMOSD is presented in Table 2.

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Table 2. Suggested MRI protocol for the diagnosis and monitoring of MS and NMOSD

Sequence	MS		NMOSD	
	Diagnosis	Monitoring	Diagnosis	Monitoring
Brain				
T2-w	Yes	Yes	Yes	If cerebral attack
FLAIR (preferably 3D)	Yes	Yes	Yes	If cerebral attack
Pre-contrast T1-w (2D)	Yes	Optional	Yes	Optional
Post-contrast T1-w (2D)	Yes	Optional	Yes	If cerebral attack
DIR or PSIR*	Yes	Optional	Optional	No
High-resolution T1-w (3D)†	Optional	Optional	Optional	Optional
SWI‡	Optional	Optional	Optional	No
DTI	Optional	Optional	Optional	Optional
Optic nerve				
Fat-Sat T2-w/FLAIR/STIR§	Optional	If optic neuritis	Yes	If optic neuritis
Fat-Sat post-contrast T1-w	Optional	If optic neuritis	Optional	If optic neuritis
Spinal cord				
≥ 2 Sagittal T2-w	Yes	Yes	Yes	If myelitis
Axial T2-w	Yes	Yes	Yes	If myelitis
Sagittal pre-contrast T1-w	Optional	No	Optional	No
Sagittal post-contrast T1-w	Yes	If myelitis	Yes	If myelitis
Axial post-contrast T1-w	Optional	Optional	Optional	Optional
High-resolution T1-w (3D)†	Optional	Optional	Optional	Optional

Modified from Wattjes et al. [10], *Lancet Neurol* 2021;20:653-670, 2021 MAGNIMS-CMSC-NAIMS consensus recommendations according to authors' personal experience.
*Sequences for cortical lesion detection may be particularly useful at the time of diagnosis given the lack of cortical lesions in NMOSD patients, †This sequence should be included if clinicians/researchers are interested in measuring atrophy, ‡Useful for the detection of the central vein sign (more common in MS) and for the identification of the paramagnetic rim, §Optional in patients with MS, unless suspected with optic neuritis. At the time of diagnosis, evidence of long lesions extending over 50% of the optic nerve or involving the optic chiasm, even if not active, may provide clues towards NMOSD diagnosis.
MRI = magnetic resonance imaging, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, MAGNIMS = Magnetic Resonance Imaging in Multiple Sclerosis, CMSC = Consortium of Multiple Sclerosis Centres, NAIMS = North American Imaging in Multiple Sclerosis, T2-w = T2-weighted sequence, FLAIR = fluid-attenuated inversion recovery, 3D = three dimensional, T1-w = T1-weighted sequence, 2D = two dimensional, DIR = double inversion recovery, PSIR = phase-sensitive inversion recovery, SWI = susceptibility-weighted imaging, DTI = diffusion-tensor imaging, Fat-Sat = fat suppressed, STIR = short tau inversion recovery

Research Contribution of MRI

Common key questions when studying the pathogenesis of autoimmune CNS disorders are:

1. What is the pathophysiology of focal inflammation?
2. Is the normal-appearing tissue involved?
3. Which are the entry routes of the pathogenic elements in the CNS?
4. Is neurodegeneration a primary or a secondary phenomenon?

In this review, we provide examples of how structural MRI provides substantial evidence to address these open issues. A flowchart summarizing the key questions in the study of autoimmune disorders and corresponding MRI proxies is shown in Figure 1. A brief summary of the main advanced techniques discussed in this article and their interpretations are presented in Table 3.

What is the Pathophysiology of Focal Inflammation? Study of Focal Lesions

Research addressing this question has primarily focused on focal lesions. In both MS and NMOSD, lesions are located in the brain, spinal cord, and optic nerve, and can involve the white matter (WM) or grey matter (GM). Although optic nerve imaging can be particularly relevant for differential diagnosis, we mainly describe the brain and spinal cord findings, given the large amount of available MRI literature.

Conventional Features of Lesions

T2-weighted images (especially when signals from the cerebrospinal fluid [CSF] are suppressed using fluid-attenuated inversion recovery [FLAIR]) are the most

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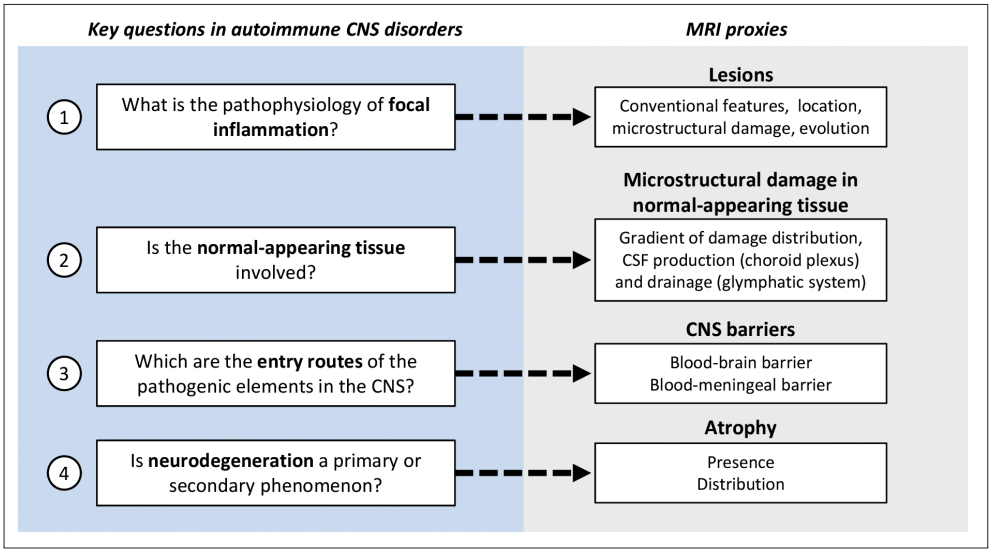

Fig. 1. Flowchart summarizing the key questions in the study of autoimmune CNS disorders with corresponding MRI proxies. CNS = central nervous system, MRI = magnetic resonance imaging, CSF = cerebrospinal fluid

Table 3. Summary of the advanced MRI techniques applied in MS and NMOSD and discussed in the current review

Indices	Meaning	Abnormal
T2-weighted and T1weighted images		
T1/T2-weighted ratio	Myelin content [200], dendritic density [201], or neurite density [202]	↓
DTI*		
Fractional anisotropy (FA)	Axonal > myelin integrity	↓
Mean diffusivity (MD)	Myelin > axonal integrity	↑
Axial diffusivity (AD)	Axonal integrity	↓↑ depending on timing
Radial diffusivity	Myelin integrity	↑
Diffusion along perivascular space index	Glymphatic function	↓
NODDI†		
Neurite density index (NDI)	Amount of neurites	↓
Intracellular volume fraction (ICVF)	Amount of neurites	↓
Orientation dispersion index (ODI)	Variability of neurite orientation (tissue complexity)	↓
Isotropic volume fraction (isoVF)	Amount of free water	↑
^{1}H-MRS		
Choline (Cho)	Cell membrane marker	↑
N-acetylaspartate (NAA)	Neuronal marker	↓
Lactate (Lac)	Anaerobic metabolism	↑
MT		
Magnetization transfer ratio (MTR)	Myelin content	↓

*DTI: provides information on tissue integrity based on the movement of water molecules. The principle is that water molecules in the white matter do not move randomly but follow a preferential direction (i.e., fractional anisotropy), that overlaps the orientation of the white matter tracts [203,204]. The higher the fractional anisotropy, the higher the integrity of axons in the white matter. In addition, the presence of macromolecules such as myelin limits the mean diffusion of water molecules, so that increased mean diffusivity is usually considered an index of demyelination (although also the presence of the axonal membranes in part limits mean diffusivity) [203,204]. Other indices indicating the status of axons and myelin are the axial and the radial diffusivity, respectively [203,204]. However, this model has some limitations, such as its poor interpretability in case of crossing fibers or tissue organization (for example, in the cortex), but also the relatively non-specificity of findings, †NODDI: this model was recently proposed to overcome the limitations of DTI, and is obtained through the acquisition of multi-shell diffusion weighted images with axial echo-planar imaging (EPI) [205]. This is a three-compartmental model where brain tissue as made of an intracellular space (i.e., within the neurites membranes), extracellular space (i.e., around neurites, which includes glial cells or neural somas), and the cerebrospinal fluid (i.e., free water with isotropic diffusivity) [205].
MRI = magnetic resonance imaging, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, DTI = diffusion-tensor imaging, NODDI = neurite orientation dispersion and density imaging, ^{1}H-MRS = portion magnetic resonance spectroscopy, MT = magnetization transfer

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sensitive for detecting hyperintense brain WM lesions [13]. A variable proportion of these lesions is hypointense on T1-weighted images, where they are called "black holes" due to their hypointense signal compared to adjacent WM [14], pathologically corresponding to areas of more severe axonal loss [15]. More advanced imaging sequences, such as double-inversion recovery, phase-sensitive inversion recovery, and T1-weighted magnetization-prepared rapid gradient-echo are needed to identify cortical lesions [10,16].

In MS, brain lesions are invariably present and known specifically to involve the periventricular areas (i.e., periventricular lesions), U-fibers or the cortex (i.e., juxtacortical/cortical lesions), and brainstem or cerebellum (i.e., infratentorial lesions) [1,16]. These locations and spinal cord involvement are listed for the assessment of dissemination in space, according to the MS diagnostic criteria [1].

Features of a typical lesion suggestive of MS have been identified. Lesions must measure at least 3-mm in size [1]. Periventricular lesions are ovoid, with the long axis perpendicular to the body of the lateral ventricles in a shape termed "Dawson's fingers" [16]. Cortical lesions are observed from the earliest stages of MS [17] and usually follow the shape of the cerebral sulci and gyri (i.e., curvilinear/worm-shaped lesions), or have an oval or wedge shape [16,18]. Their identification has so far been hampered by the low inter-rater agreement of physicians, despite international guidelines [19] and the non-uniform availability of such pulse sequences in all clinical centers [10]. Nevertheless, their assessment may be particularly relevant for clinical outcomes because they represent risk factors for cognitive impairment [20] and secondary progression [21].

In NMOSD, brain MRI was considered normal until recent years when studies revealed a significant incidence of T2-hyperintense lesions in this disease, with a frequency between 43%–70% at disease onset [22-24]. Several features are considered typical of NMOSD, including location along the ependymal layer of the lateral and fourth ventricles (periependymal lesions), diencephalic region, corticospinal tract, and dorsal brainstem (possibly adjacent to the fourth ventricle or including the area postrema). A Balo-like appearance has also been described [25], although it was recently demonstrated to be rare [26]. Several studies have assessed cortical lesions in patients with NMOSD. Cortical lesions were not identified in independent cohorts of Caucasian and Afro-Caribbean patients at 3.0 T [27,28], 7.0 T [29], or pathologically [30], although a few investigations reported cortical lesions among Asian patients with NMOSD, ranging between 3%–11% [31,32]. A pathological study reported that cortical damage occurs in NMOSD with neuronal loss, AQP4-changes in astrocytes, and meningeal inflammation in the absence of focal cortical demyelination [30].

In terms of lesion-size, NMOSD lesions can be large hemispheric (i.e., transverse diameter > 3 cm) or small non-specific (< 3 mm) [25]. Their shapes are variable and include linear, spindle-like, or radial-shaped aspects, following the main WM tracts [25].

Spinal cord lesions can be particularly useful for differentiating MS from NMOSD, given their tendency to be short in the first disease and long (i.e., extending over three contiguous vertebral segments) in the latter [25]. Examples of typical lesions and their locations in MS and NMOSD are shown in Figure 2.

The utility of lesion location for the differential diagnosis of MS and NMOSD was proven by several MRI-based algorithms, which highlighted the specificity of periventricular and juxtacortical/cortical lesions for MS and periependymal lesions for NMOSD [28,33,34]. Table 4 summarizes the typical features of MS and NMOSD lesions together with the MRI-based algorithms proposed for the differential diagnosis of the two disorders.

Surveillance MRI to detect new or active lesions over time is the most widely used paraclinical tool for the assessment of treatment efficacy in MS [35], but not in NMOSD, owing to the extremely low rate of asymptomatic lesion (3.4%) development [12].

Lesion Location

Lesions in MS envelop the perivenular vessels running perpendicular to the ventricular system, as revealed by pathological studies showing lympho-monocytic infiltrates along these venules [36]. From an imaging perspective, the implementation of 3D MRI pulse sequences sensitive to iron, such as T2*-weighted gradient echo sequences (T2*), especially with segmented echo-planar imaging (EPI) and its variation susceptibility-weighted imaging (SWI), together with post-processing, allows the visualization of veins running through MS lesions [37]. Sensitivity to this sign can be enhanced by acquisition at a high (3.0 T) or ultra-high (7.0 T) field strength and by the administration of contrast agents [37]. According to the North American Imaging in Multiple Sclerosis Cooperative guidelines, the "central vein sign" is defined as a thin linear area of T2*-hypointensity running in the center of a WM lesion on a

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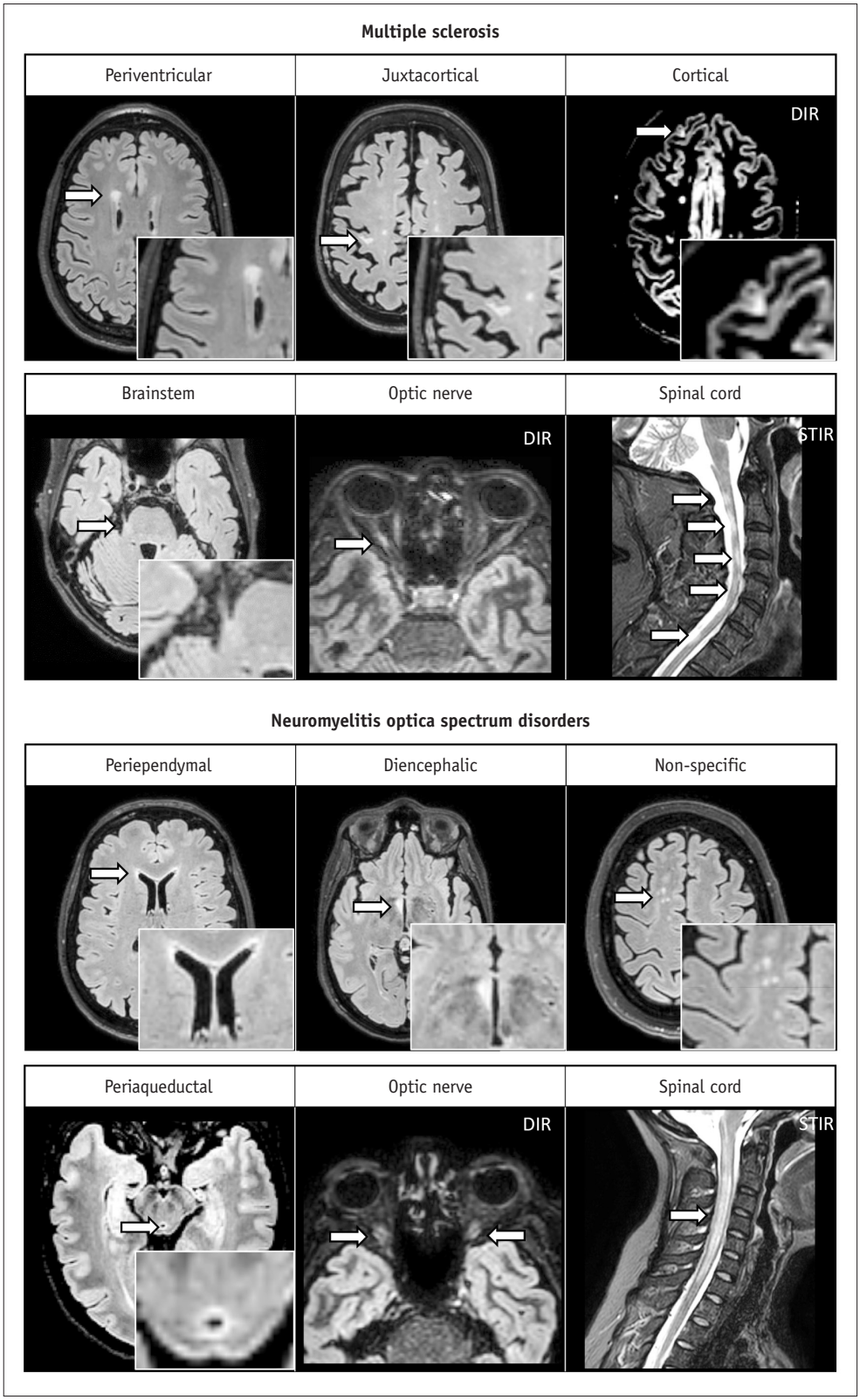

Fig. 2. Examples of typical lesion locations and appearance at MRI in patients with MS and NMOSD. Lesions are indicated by arrows. Unless otherwise specified, brain images are shown on FLAIR (axial view). Optic nerve lesions are visible on double inversion recovery (axial view), and spinal cord lesions are shown on short tau inversion recovery (sagittal view). MRI = magnetic resonance imaging, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, FLAIR = fluid-attenuated inversion recovery, DIR = double inversion recovery, STIR = short tau inversion recovery

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Table 4. Typical features of lesions in MS and NMOSD

Lesion features	MS	NMOSD
Brain		
Shape	Ovoid (Dawson's fingers)	Variable
Location	Periventricular	Periependymal
	Juxtacortical/Cortical	Diencephalic
		Corticospinal tract
	Brainstem	Dorsal brainstem
Central vein sign	> 50% of lesions	Rare
Iron rim	Present	Absent
Optic nerve		
Site	Unilateral	Bilateral
Length	Short	Long‡
Cord		
Length	Short	Long§
Location	Peripheral	Central
MRI algorithms	1 of 3 criteria*	2 of 5 criteria†

*At least one of the following: (1) lesion adjacent to the body of the lateral ventricle and in the inferior temporal lobe, (2) a subcortical U-fiber lesion, and (3) a Dawson's finger-type lesion [34], †At least one of the following: (1) longitudinally extensive lesion in the spinal cord, (2) periependymal lesion of the lateral ventricles; absence of (3) juxtacortical/cortical U-fiber lesions, (4) Dawson's finger-type lesions, and (5) ovoid periventricular lesions [28], ‡At least 50% of the optic nerve length, §At least three consecutive vertebral segments.
MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, MRI = magnetic resonance imaging

sagittal cut, or a dot-like hypointensity on a transverse cut [37]. Numerous studies have evaluated the frequency of the central vein sign in different WM disorders, including MS, NMOSD, myelin-oligodendrocyte antibody-associated disease, chronic small-vessel disease, Sjogren's syndrome, Bechet's disease, and migraine [38-42]. There is substantial agreement that the central vein sign in at least 35%–55% [38-41] of lesions identifies patients with MS. Less time-consuming analyses, such as the detection of at least three lesions showing the central vein sign, demonstrated a similar diagnostic performance [40,43].

The rarity of the central vein signs in NMOSD lesions is evidence of a different pathophysiology of the disorder [40,41,44]. Periependymal lesions are the most specific type of NMOSD [28]. One study demonstrated that the periependymal region is characterized by high AQP4 expression, suggesting that lesion location in NMOSD is, at least in part, due to differential expression of a target antigen across CNS regions [45]. However, this does not apply to lesions in the corticospinal tract, which is conversely known to be an AQP4-poor region of the brain [25]. This may be due to the concomitant presence of other favorable factors, such as complement expression, in areas with a high probability of brain lesions [46].

Microstructural Damage and Evolution of WM and Spinal Cord Lesions

The characterization of lesions using multimodal MRI pulse sequences has revealed a high degree of heterogeneity in tissue disruption and repair. Conventional imaging (e.g., T2- and pre-/post-contrast T1-weighted quantitative or non-quantitative images) and advanced imaging (e.g., magnetization transfer [MT], diffusion-weighted imaging, diffusion-tensor imaging [DTI], T2*-weighted imaging, EPI, and proton magnetic resonance spectroscopy [^{1}H-MRS]) have been used for this purpose in MS. Despite technical heterogeneity, there is substantial consensus regarding the dynamics and characterization of lesional changes.

Four stages are recognized in the natural history of MS lesions: 1) pre-clinical, 2) acute, 3) reparative (with different efficiency of recovery mechanisms), and 4) chronic. During the pre-clinical stage, no tissue abnormalities were visible with conventional non-quantitative sequences. Nevertheless, pre-lesional changes can be measured in normal-appearing WM at the site of an upcoming lesion, months to weeks before its appearance. These are mainly represented by perfusion/permeability changes and demyelination, as suggested by increased perfusion [47], increased diffusivity (apparent diffusion coefficient and mean diffusivity [MD]) [48,49], decreased magnetization transfer ratio [MTR] [50], and increased choline levels (Cho, at ^{1}H-MRS) [51,52].

In the acute phase, a lesion is detectable on T2-weighted images as a new hyperintense focal area, which is usually enhanced on post-contrast T1-weighted images. Intralesional damage shows the progression of demyelination (increased MD, radial diffusivity [RD], Cho, and lactate, and decreased MTR) [51,53-57], development of variable degrees of axonal damage (decreased fractional anisotropy [FA] and N-acetylaspartate) [51,54-58] and metabolic changes (increased lactate) [55,57,59]. Finally, the lesion undergoes a phase of progressive tissue recovery [55], with enhanced resolution and variable normalization of the abovementioned parameters (especially MTR) over seven months [60]. Lesions with lower MTR [53] and higher RD [56] are likely to become chronic black holes. At the end of this period, the lesion appeared smaller on T2-weighted images, but rarely disappeared (5%) [61].

The neurite orientation dispersion and density imaging

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(NODDI) technique has so far been applied only cross-sectionally to lesions, showing a reduced neurite density index (NDI) [62,63], orientation dispersion index (ODI) [62], and intracellular volume fraction (ICVF) [64], together with an increased isotropic volume fraction (isoVF) [62,64].

In the chronic phase, > 50% of lesions may reveal subtle chronic inflammatory activity with persistent local inflammation [65]. These lesions are known as chronic-active, slowly enlarging or smoldering. On MRI, chronic-active lesions may show a peripheral paramagnetic rim, which usually persists over time [66,67] (although in some cases, it disappears after years) [68] and histologically corresponds to a layer of iron-rich macrophages at the edge of the lesion [66]. Alternatively, they can be automatically identified on serial conventional MRI (i.e., T2- and T1-weighted images) by calculating the Jacobian of the nonlinear deformation field between time points [69]. Lesions showing a progressive growth identified by a voxel-wise expansion of at least 12.5% per year are selected with this approach [69,70]. However, this methodology likely identifies only a subset of lesions with persistent paramagnetic rims because progressive enlargement does not occur in all lesions and is usually more common in patients with progressive disease [70].

These lesions have been observed in patients with worse disability or faster progression [69,71], demonstrating progressive intralesional tissue damage [72]. Lesions with persistent peripheral rim are characterized by more severe intralesional damage, with prolonged lesional T1-relaxation time [72] and more severe reduction in NDI [63].

Little evidence is available regarding NMOSD, and no studies to our knowledge has provided longitudinal data on intralesional microstructural abnormalities. Cross-sectional studies have demonstrated inconsistent results with NMOSD brain lesions characterized by a worse reduction in FA [73], milder reduction in axial diffusivity [64,73], MD [64,73], and RD compared to MS [64], or no significant changes in FA [64] or RD [73] compared to MS or healthy subjects. Using NODDI, patients with NMOSD showed reduced ODI, increased isoVF, and normal ICVF compared to healthy controls [64]. In the cord, increased intralesional RD was found in NMOSD compared with that in MS [74]. Figure 3 shows examples of lesion appearance on conventional and advanced MRI sequences in patients with MS and NMOSD.

Therefore, no conclusions can be drawn regarding NMOSD due to a lack of strong evidence, and additional studies are needed to improve our understanding of intralesional microstructural abnormalities and their dynamics. Nevertheless, lesion evolution on conventional imaging provides clues about the different pathophysiologies of NMOSD. For instance, the frequency of lesion resolution, although low, was twice that of MS (10%) [61]. Preliminary data highlight that NMOSD lesions do not exhibit a peripheral paramagnetic rim at 7.0 T [29,75] and 3.0 T [76], suggesting a lack of chronic active inflammation.

Microstructural Damage of Cortical Lesions

Characterization of the microstructure of cortical lesions has long been considered challenging because of the poor fit of the DTI model to the disruption of cortical tissue within lesions. In fact, a consistent finding among multiple independent studies in MS is a paradoxical increase in FA compared with a surrounding normal-appearing GM [77-81], promoting different hypotheses. Two pathology-MRI studies recently resolved this unexplained MRI finding [82,83] by demonstrating increased cellular density [82] and tissue reorganization [83] within cortical lesions.

Under physiological conditions, diffusion anisotropy in the cortex is mainly due to the normal representation of axons perpendicular to the cortical surface (perpendicular axons connecting the cortex to the WM) [83]. Remote WM lesions can reduce the number of perpendicular axons in the cortex through secondary retrograde degeneration, which explains the FA reduction observed in normal-appearing cortex [83]. Additionally, loss of axons running parallel to the cortical surface was observed within cortical lesions. Pseudonormalization of the ratio between perpendicular and parallel axons results in a paradoxical increase in FA compared with non-lesioned tissues [83].

This pathophysiological model was recently replicated in a study of the cortex using the NODDI model. The findings showed reduced ICVF (a proxy of neurite density) [84] in both lesioned- and normal-appearing cortices but reduced ODI (i.e., neurite orientation and dendritic arborization complexity) [84-86] only within cortical lesions [84].

Is the Normal-Appearing Tissue Involved? Study of Microstructural Abnormalities

Microstructural abnormalities can be detected using MRI pulse sequences, which can interrogate the microstructural features of tissues (Table 3). In MS, microstructural abnormalities involve both lesioned and normal-appearing tissues, with evidence of different degrees of demyelination (i.e., increased MD) and axonal damage (i.e., decreased FA)

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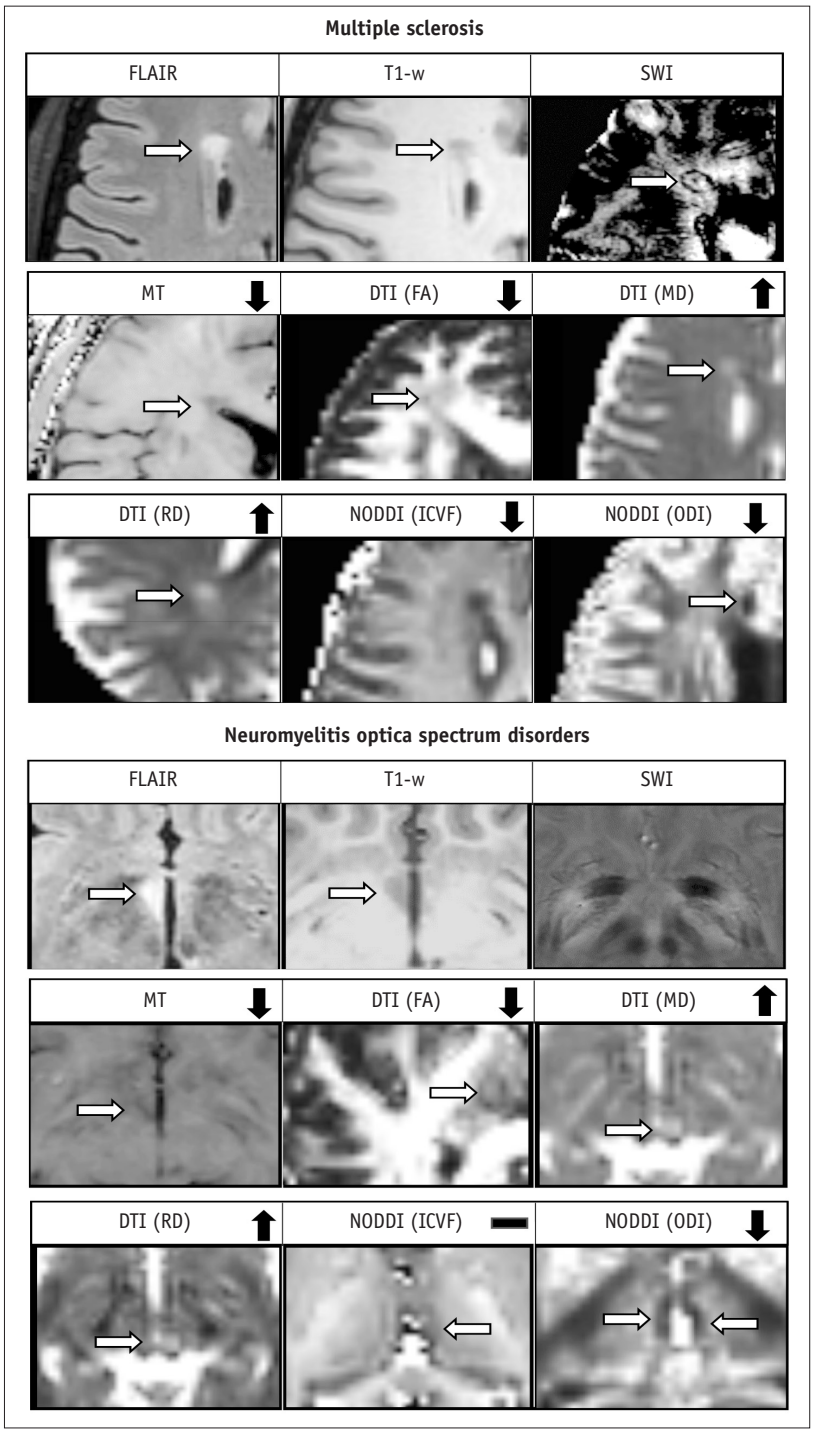

Fig. 3. Examples of MRI lesions on conventional and advanced sequences in patients with MS and NMOSD. Lesions are indicated by white arrows and shown in axial view. Black arrows indicate increase or decrease. Black horizontal line indicates inconsistent change. MS: hyperintense periventricular lesion on FLAIR, with corresponding hypointensity on T1-w; periventricular lesion with peripheral rim on SWI; periventricular lesion with reduced signal on MT map; extensive white matter lesion showing decreased FA; periventricular lesions with increased MD, increased RD, and decreased ICVF; juxtacortical lesion with decreased ODI. NMOSD: Diencephalic lesion hyperintense on FLAIR, with corresponding T1-hypointensity. The lesion does not show any paramagnetic effect on SWI and is hypointense on the MT map. The thalamic lesion shows decreased FA, periaqueductal lesion showing increased MD and RD, bilateral diencephalic lesion showing reduced ODI, and reduction of ICVF only on the left side. MRI = magnetic resonance imaging, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, FLAIR = fluid-attenuated inversion recovery, T1-w = T1-weighted sequence, SWI = susceptibility-weighted imaging, MT = magnetization transfer, FA = fractional anisotropy, MD = mean diffusivity, RD = radial diffusivity, ICVF = intracellular volume fraction, ODI = orientation dispersion index, NODDI = neurite orientation dispersion and density imaging, DTI = diffusion-tensor imaging

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[48,87-90]. Similar findings have been reported in the spinal cord, independent of lesions [91]. Neuroaxonal damage (decreased ICVF and NDI) [63,92] and loss of physiological architecture in the normal-appearing white matter (NAWM) (ODI reduction) [92] were also significant in MS patients [92] with NODDI.

Normal-appearing WM abnormalities are controversial in NMOSD, where studies have found either diffuse damage [73,93], abnormalities restricted to the WM tracts potentially undergoing secondary degeneration (i.e., in the visual pathway and sensorimotor system) [94], or no damage [95]. In the spinal cord, patients with NMOSD showed reduced FA, increased MD, and reduced MTR compared with those in healthy controls, but are similar to MS [91]. Although the study did not consider lesioned and non-lesioned tissues separately, these abnormalities were absent in patients with no corresponding spinal cord lesions [91]. Table 5 and Figure 4 summarize these studies.

CSF-in Gradient of Damage

Although brain microstructural abnormalities are diffuse in MS, several independent investigations have demonstrated that such damage is more severe closer to periventricular areas. This was proven using different techniques, including the MTR [96-98], DTI [73,99,100], and T1/T2-weighted ratio [100], both in normal-appearing WM [73,96-99] and in the thalamus [100] (Fig. 5).

Abnormalities have been detected from the earliest phases of MS, including in patients with clinically isolated syndrome [99] and pediatric MS [100,101], and are more severe in patients with CSF-restricted oligoclonal bands [99]. Similarly, using T2*-weighted images on 7.0 T MRI, researchers found a progressive gradient of demyelination, starting from the external layers of the cortex and expanding to the deeper cortical layers [102].

These findings reinforce the hypothesis that the pathogenic element of damage in MS is found in the CSF, which is in contact with the periventricular areas and external cortex [103]. To the best of our knowledge, only one DTI study has investigated a gradient of damage similar to MS in patients with NMOSD and detected diffuse abnormalities (increased MD and reduced T1/T2-weighted ratio, but normal FA) in the periventricular normal-appearing WM with no clear regional distribution [73]. Other independent studies have demonstrated abnormalities in the NAWM in terms of diffusivity (mean, axial, and radial) without FA reduction [64,93]. These findings are in line with a recent pathological investigation, which showed that NMOSD-associated astrocytopathy is diffuse and not restricted to lesioned tissues [104] without diffuse axonal damage.

Abnormal CSF Production and Drainage

Following these observations, the choroid plexus, one of the main elements of the blood-CSF barrier [105], has recently gained attention. The choroid plexus is deputed to CSF production, is located along the floor of the lateral ventricles and roof of the third and fourth ventricles, and regulates immune trafficking within the CNS [106]. It can be

Table 5. Microstructural damage and atrophy in MS and NMOSD

Features	MS	NMOSD
Microstructural damage		
Present	Yes	Yes
Affecting the normal-appearing tissue	Yes	Controversial
Type of abnormalities		
Axonal damage	Yes	Potentially
Demyelination	Yes	Controversial
Distribution	Diffuse (CSF-in gradient)	Diffuse or restricted to secondary neurodegeneration
Atrophy		
Present	Yes	Yes
Distribution		
White matter	Yes	Controversial
Grey matter	Yes	Controversial
Cortex	Yes	Yes (secondary neurodegeneration)
Hippocampus	Yes	Yes
Thalamus	Yes	Yes

MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, CSF = cerebrospinal fluid

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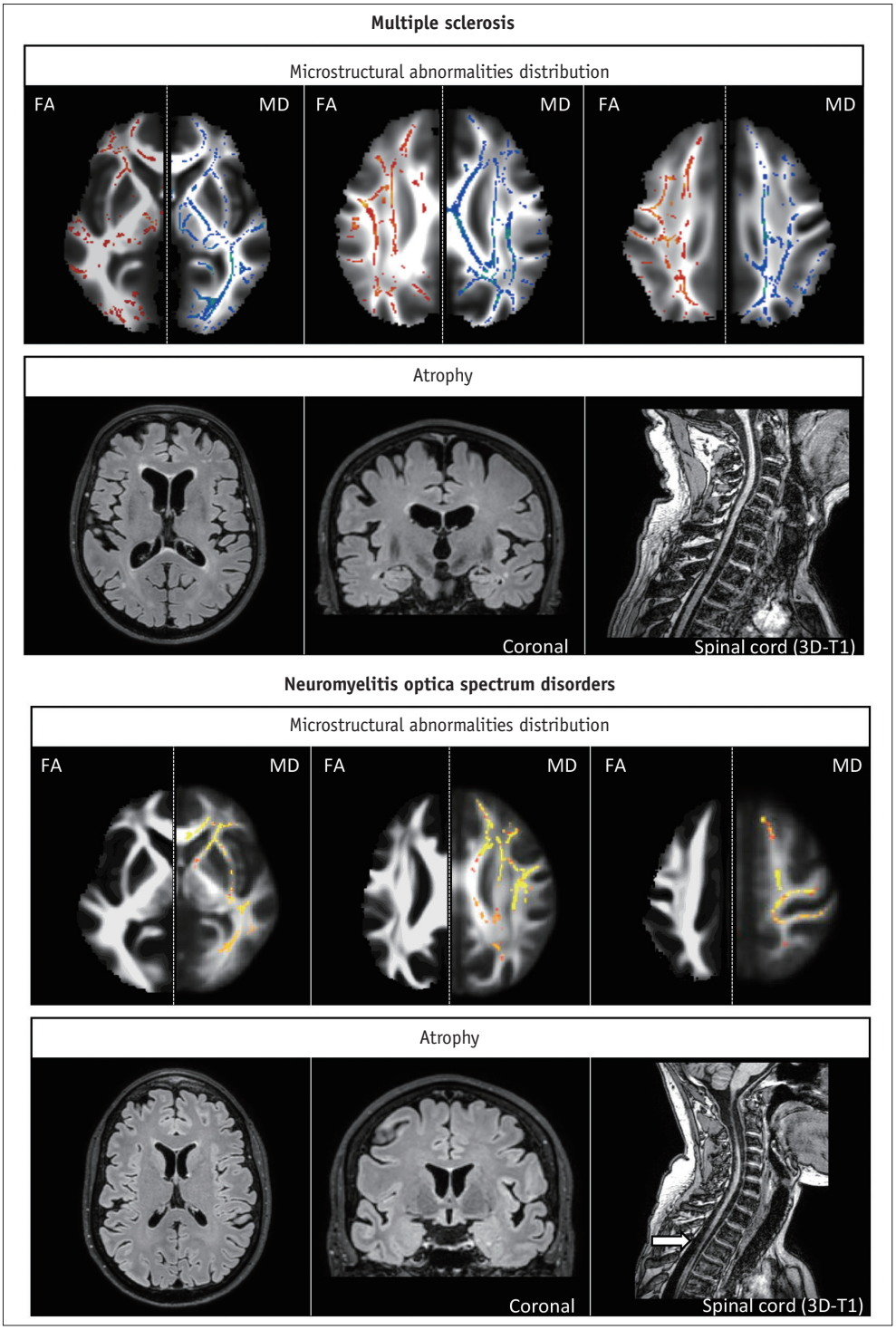

Fig. 4. Examples of MRI showing microstructural damage and atrophy in patients with MS and NMOSD. Top row of multiple sclerosis and neuromyelitis optica spectrum disorder: Microstructural damage is shown using the result of a prototypical between-group comparison of white matter damage in patients compared to a group of matched healthy controls using TBSS. Images are shown in axial view. MS: patients with MS have widespread reduction of FA (red) and increased MD (blue) compared to those in controls. NMOSD: patients with NMOSD have normal FA and diffuse increase of MD (yellow to orange). Bottom row of multiple sclerosis and neuromyelitis optica spectrum disorder: Examples of brain and spinal cord atrophy in patients with MS and NMOSD. Unless otherwise specified, brain images are shown in axial view on fluid-attenuated inversion recovery images. MS: significant ventricular enlargement, sulcus widening, and diffuse spinal cord atrophy. NMOSD: milder example of brain atrophy with significant focal volume loss in the spinal cord, corresponding to a longstanding lesion (arrow). MRI = magnetic resonance imaging, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, TBSS = Tract-Based Spatial Statistics, FA = fractional anisotropy, MD = mean diffusivity, 3D-T1 = 3-dimensional T1-weighted image

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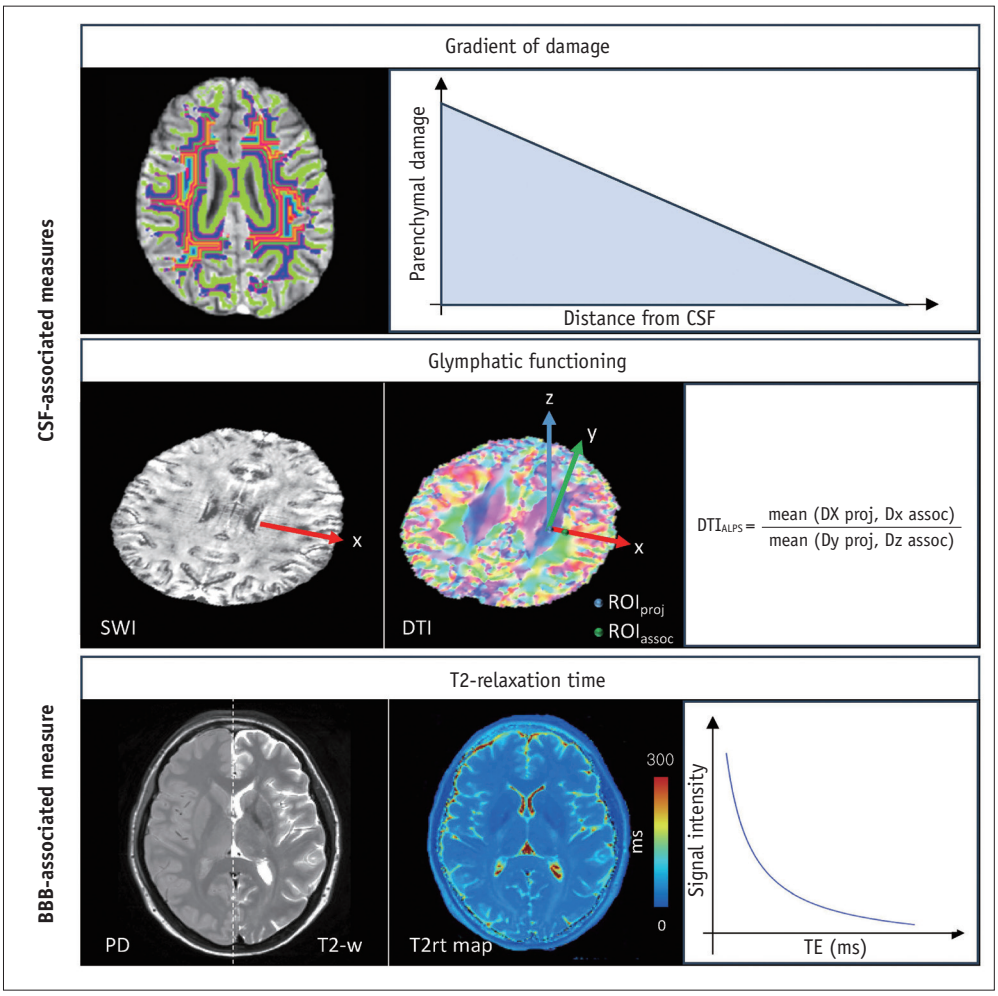

Fig. 5. Schematic representation and brief explanation of CSF- and BBB-associated measures cited in the manuscript. Colors at first row indicate brain tissue bands. Damage gradient measurement can be done by dividing the brain tissue into concentric bands, starting from the CSF-parenchymal interface estimated as a function of the geodesic distance from the ventricular system; as shown in the graph, in MS parenchymal damage is more severe closer to the CSF compartment. Glymphatic function can be assessed by measuring the DTI_{ALPS} index: SWI is used to identify the brain slice where periventricular veins run perpendicular to the ventricular system. Two ROIs are then placed on projection and associative fibers on the corresponding slice of a color-coded principal diffusion direction map. The DTI_{ALPS} index is calculated as the ratio between diffusivities perpendicular to fibers and parallel to veins, and those perpendicular to both fibers and veins [118]. The example provided refers only to the ROI on projective fibers. The T2-relaxation time measures the constant magnetization decay on the transverse plane, which may be used as a proxy for water content. It can be calculated using at least dual-echo sequences, assuming a monoexponential decay. Red, green and blue arrows at middle row indicate directions perpendicular (x and y) and parallel (z) to projective fibers. CSF = cerebrospinal fluid, BBB = blood-brain barrier, MS = multiple sclerosis, DTI_{ALPS} = diffusion along perivascular spaces index, SWI = susceptibility-weighted imaging, ROI = region of interest, DTI = diffusion-tensor imaging, proj = projective, assoc = associative, PD = proton density, T2-w = T2-weighted image, T2rt = T2-relaxation time, TE = echo time

easily measured on high-resolution T1-weighted images with excellent interrater agreement [107]. Compared with healthy controls, patients with MS have an increased volume of the choroid plexus [108-111], even after a first clinical attack [112] and during childhood [107]. This alteration seems specific to MS, as it has not been observed in patients with other neurological disorders, including migraine and NMOSD [110]. In most studies, increased choroid plexus volume was associated with more severe disability [108, 109] and relapse [109,111]. From an imaging perspective, associations were found between inflammatory and neurodegenerative indices, including T2-hyperintense and gadolinium-enhancing lesions [107-111], brain atrophy [107,108,113], slowly expanding lesions [113], and poor periventricular remyelinating capacity, in one positron emission tomography (PET)-MRI investigation [114]. These results provide additional evidence regarding the pathogenic role of CSF in MS-related brain damage.

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Another hypothesis is that CSF-mediated damage is favored by impaired drainage through the glymphatic system. This clearance system runs through the periventricular spaces, where CSF reaches the periarteriolar spaces, flows in the brain interstitium, and is then collected back at the perivenular level to eventually drain into the meningeal vessels [115]. A few studies have investigated the glymphatic function in MS using PET imaging [116], or the DTI-based method [117] developed by Taoka et al. [118], which measures an index of diffusivity along the perivascular spaces. This methodology is based on two assumptions. First, the glymphatic system runs along vessels that can be visualized with MRI using SWI. Second, water diffusivity in the brain parenchyma follows the main direction of WM tracts. Therefore, diffusivity along veins can be easily measured on brain slices where veins are perpendicular to the ventricular bodies and there are two major WM tracts (the associative and projective fibers) that cross a plane orthogonal to the veins [118] (Fig. 5).

Patients with MS have reduced glymphatic functioning [116,117], especially progressive patients [117], which is correlated with more severe disability, longer disease duration, greater WM lesion volume, and brain atrophy [117]. Using a similar approach, reduced glymphatic function was observed in two independent cohorts of patients with NMOSD [119]. In this case, it was associated with more severe disability and the disease itself, but not with disease duration or measures of brain atrophy [119]. The similarities and discrepancies between these two studies highlight the fact that glymphatic function may be impaired in inflammatory CNS disorders. However, they also demonstrated that this process worsens over time in MS, suggesting that it might be secondary to inflammatory damage (e.g., lymphocyte infiltrates and astrocyte damage within a lesioned tissue). It promotes a vicious circle of inflammation and neurodegeneration by increasing the time of contact between the brain tissue and pathogenic factors originating from CSF, cytokines, and reactive oxygen species.

Glymphatic impairment is likely primarily associated with the disease itself in NMOSD. In fact, AQP4 water channels are the main drivers of fluid transport from the perivascular compartment to the brain interstitium, and their absence is associated with a 60% reduction in glymphatic flow [120,121]. Therefore, AQP4 loss observed in the tissues of patients with NMOSD [122] may lead to primary glymphatic impairment. However, it is worth mentioning that glymphatic impairment was reported in numerous neurological conditions, such as Parkinson's disease, Alzheimer's disease, and idiopathic normotensive hydrocephalus [123]. Therefore, this finding is not specific to CNS inflammation. Furthermore, the existence of a glymphatic system in humans remains a topic of debate, and such diffusion abnormalities may be related to other processes.

Which are the Entry Routes of Pathogenic Elements in the CNS? Study of CNS-barriers

Besides the CSF, breakdown of the main CNS barriers, such as the blood-brain barrier and blood-meningeal barrier, are considered possible entry routes of pathogens into the CNS.

Blood-Brain Barrier Damage

Damage to the blood-brain barrier is a possible entry route for autoreactive cells or antibodies into the CNS. The blood-brain barrier is a multilayer structure that encompasses endothelial cells, lamina basale, pericytes, and astrocytes [124].

According to the most recent hypothesis, the pathogenesis of MS is biphasic. First, there is a pulsed blood-brain barrier breakdown, which accounts for CNS invasion by autoreactive T cells ("outside-in stage"). Further, changes to the blood-brain barrier cause a compartmentalization of inflammation within the CNS ("compartmentalized" stage) [5]. This stage is believed to favor neurodegeneration and may play a role in the transition to a secondary progressive phase of MS.

Gadolinium enhancement of lesions on post-contrast T1-weighted images is the MRI correlate of blood-brain barrier disruption in new lesions [125], and is typical of patients with relapsing-remitting MS, especially in young patients [126] and those with short disease duration [127]. Acute blood-brain barrier dysfunction is usually transient and has a median duration of two weeks [128]. Advanced post-contrast imaging, such as dynamic contrast enhancement (DCE)-MRI, which is more sensitive to subclinical levels of blood-brain barrier leakage, has demonstrated increased blood-brain barrier permeability, even in the normal-appearing WM of clinically isolated syndrome patients [129] and in patients with progressive MS [130]. In patients with clinically isolated syndrome, it was associated with an 8.5 times greater risk of conversion to MS over two years [129]. The main patterns of gadolinium enhancement classically described in MS lesions are ring-like (especially open ring) and nodular [131]. Additionally, DCE-MRI can be used to assess the dynamics of gadolinium enhancement patterns over time by collecting multiple postcontrast images. In line

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with the lack of histological differences between nodular- and ring-enhancing lesions, this technique showed that these enhancement patterns do not represent different pathophysiological processes, but depend on the timing of image acquisition relative to gadolinium injection and lesion size [127]. On the time of a single MRI acquisition, smaller lesions usually demonstrate a pattern of nodular enhancement with centrifugal expansion, while larger lesions have a ring-like pattern of enhancement, spreading centripetally and becoming nodular (in the case of small lesions) or nearly nodular (with a centrally spared core) within minutes [127]. When enhancing lesions are followed-up with a subsequent scan over five days, initially nodular lesions with centrifugal enhancement usually grow in size and show a pattern of centripetal enhancement. Based on these observations, the authors postulated that the earliest blood-brain barrier damage occurs in the central vein, as seen on MRI as centrifugal enhancement in small nodular lesions. Using a 7.0 T scanner, the central vein was confirmed as the starting point of blood-brain barrier leakage by demonstrating that the central vein sign was present in most lesions showing centrifugal enhancement (73%) [132]. Later, as the lesion grows, the blood-brain barrier opens in the corresponding peripheral vessels at the edge of the lesion, with a consequent switch in the enhancement pattern from centrifugal to centripetal. The disappearance of centrifugal enhancement at this stage is likely due to closure of the blood-brain barrier around the central vein or hypoperfusion of the lesion core, which limits the quantity of gadolinium reaching the center of the lesion. Tissue damage within the lesion allows gadolinium to diffuse into the lesion [127]. However, switching from centrifugal to centripetal enhancement is not a requisite process and occurs in approximately 50% of lesions [66]. Concomitant acquisition of susceptibility-weighted phase images at 7T demonstrated that the ring of centripetal enhancement is colocalized with the peripheral paramagnetic rim [66,133], which can be transient (i.e., resolves within three months after the disappearance of enhancement) or persistent over time (55% of lesions with centripetal enhancement). Paramagnetic rim persistence is a hallmark of chronic inflammation at the edge of a lesion, which helps identify the subset of chronic active lesions that are believed to be involved in disease progression [66]. Therefore, gadolinium enhancement not only indicates increased blood-brain barrier permeability but also a link between acute lesion formation and compartmentalized inflammation.

As previously mentioned, NMOSD is a primary astrocytopathy with secondary demyelination caused by an autoantibody targeting AQP4. Astrocytes are constituents of the blood-brain barrier [124], and the AQP4 water channel is the main regulator of CNS water homeostasis [134]. According to pathological studies, astrocyte abnormalities are not restricted to lesioned tissues, but are diffusively present [104]. Given the involvement of both astrocytes and AQP4 in NMOSD, it is evident that blood-brain barrier permeability and water homeostasis may be impaired by astrocyte damage or death and AQP4 downregulation or loss [73].

In line with this, sera from patients with NMOSD can disrupt the blood-brain barrier in experimental models [135]. From an imaging perspective, NMOSD gadolinium-enhancement patterns on brain post-contrast T1-weighted images usually differ from those of MS. In the brain parenchyma, enhancement can have a linear shape following the ependymal layer (periependymal enhancement) or be poorly marginated, patchy, or inhomogeneous, the so-called "cloud-like" enhancement [25,136]. Asymptomatic optic nerve enhancement has been reported in 17% of patients with NMOSD, mainly at the site of prior optic neuritis [137]. Increased blood-brain barrier permeability in small vessels and subclinical or intermittent blood-brain barrier leakage have been suggested as pathophysiological explanations [136,137]. During the acute phase of NMOSD, additional radiological findings suggesting increased blood-brain barrier permeability can be observed on conventional MRI sequences, such as the posterior reversible encephalopathy syndrome [138] and brighter-spotty lesions in the spinal cord, characterized by a T2-signal intensity that is at least equal to that of the CSF [139,140]. In both cases, lesions mostly disappear with resolution of the attack [138,139], indicating a transient acute process rather than tissue disruption.

No studies applying DCE-MRI to measure blood-brain barrier permeability have been conducted in patients with NMOSD. However, brain water content was indirectly measured in patients with NMOSD and compared to healthy controls by measuring the T2-relaxation time (i.e., the constant magnetization decay on the transverse plane, which reflects the movement of water protons and increases with higher water content) [141,142] (Fig. 5). Patients with NMOSD had a subclinical increase in brain water in normal-appearing WM, GM, and the deepest GM nuclei [142]. When patients were divided into two groups according to

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disease activity, active patients (those who had a relapse within one month before or after MRI acquisition) showed higher levels of brain water in the normal-appearing WM and GM. The T2-relaxation time (i.e., water content) in normal-appearing WM was the only predictor of disease activity [142]. In this study, the T2-relaxation time closely acted like serum glial fibrillary acidic protein (GFAP, a marker of astrocyte damage) in patients with NMOSD enrolled in the N-MOmentum trial, whose levels increased within a week prior to relapse [143]. Although this might support the association between astrocytic damage at the blood-brain barrier and water imbalance, studies correlating T2-relaxation time with GFAP levels are needed to confirm this hypothesis.

Blood-meningeal Barrier Damage

The origin of cortical demyelination in MS has long been debated. In a study assessing the type and dynamics of gadolinium enhancement in acute MS lesions, enhancing lesions showed no enhancement corresponding to the GM, leading to open-ring patterns of enhancement in juxtacortical lesions [127]. The lack of enhancement at the cortical edge supported the hypothesis that blood-brain barrier disruption does not significantly contribute to cortical lesion formation, which is likely associated with subpial demyelination in the context of meningeal inflammation [144].

Leptomeningeal enhancement, which corresponds to blood-leptomeningeal barrier breakdown, is a relatively common but non-specific finding in MS [145]. It can be visualized on post-contrast T2-FLAIR images, or to a lesser extent, on post-contrast T1-weighted images; increasing field strengths from 1.5 to 7.0 T improve its detectability [146]. The appearance of leptomeningeal enhancement can be nodular or laminar/spread-and-fill [146], which is not observed in healthy controls [147]. Only one study has assessed the pathological correlates of this imaging feature and described subpial demyelination with foci of leptomeningeal perivascular inflammation and lymphomacrophagic infiltrates in areas of enhancement [148].

Using quantitative T2* imaging at 7.0 T, another group found a gradient of cortical damage involving the outer cortical layers at early disease stages that progressively expanded to the deep cortex [102], which could be potentially related to meningeal inflammation [149].

According to a recent meta-analysis, the frequency of leptomeningeal enhancement in MS is approximately 30%, which is almost twice higher in progressive MS (39%) than in relapsing-remitting MS (19%) [146]. The foci of leptomeningeal enhancement usually persist over time [148,150-153], and are not significantly altered by the administration of disease-modifying drugs [151-153].

Overall, their associations with older age or longer disease duration [148,150,154], worse motor disability [148,154,155], and more severe cortical atrophy [147,154,156-159] are mainly consistent across different studies, whereas their correlation with cortical lesions is controversial [157,159].

Together, these observations suggest a role for leptomeningeal enhancement in chronic and diffuse meningocortical damage that is likely independent of focal cortical demyelination [160].

Few studies have investigated leptomeningeal enhancement in NMOSD using similar pulse sequences. In NMOSD, leptomeningeal enhancement is linear or extensive, can involve either the brain or spinal cord, and has invariably been observed during acute relapses [161,162], usually associated with contiguous periependymal or parenchymal enhancement [161]. In contrast to MS, in which leptomeningeal enhancement is longstanding and not modified by treatment (see above, earlier in the same paragraph), its association with the acute phase of NMOSD is further supported by its disappearance after therapy [162]. The prevalence of this finding was 6%, which was significantly lower than in MS [146]. The CSF of NMOSD patients with leptomeningeal enhancement was characterized by pleocytosis [161]. Positive AQP4-IgG was found in patients with this radiological finding [161,163], suggesting that the breakdown of the blood-meningeal barrier may be an additional route for antibody entry into the CNS.

Is Neurodegeneration a Primary or a Secondary Phenomenon? Study of Atrophy

Inflammation and neurodegeneration eventually lead to brain atrophy, which has been extensively reported in several neurological disorders. The normal physiological rate of brain volume loss with aging is estimated to be between 0.1%–0.3% per year [164]. Higher rates of atrophy (0.46%–1% per year) have been observed in patients with MS [165-167], leading to the emerging concept of accelerated brain aging [168].

In MS, atrophy involves both the WM and GM, with higher rates in GM associated with disability progression [169,170]. The hippocampi [171-175] and thalami

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[101,176-178] are among the structures that suffer from volume loss since the earliest phases of the disease, often with detrimental implications for cognition [171,175] and disability [179,180]. Atrophy development in MS is at least partly due to the presence of WM lesions [181], although evidence of its amount and extent from the earliest stages of the disease [182] suggests concomitant participation of a primary neurodegenerative process. Similarly, spinal cord atrophy, which is relevant to motor disability, has been extensively demonstrated in patients with MS [91,183-186], with only a partial overlap with the presence and location of lesions [91,185].

The huge number of studies on brain atrophy in MS have prevented a comprehensive summary of the literature. For the purposes of this review, we focused on a phenomenon with important implications for clinical trials: evidence of volumetric variations in response to inflammation. Pseudohypertrophy has been detected in patients with clinically isolated syndromes close to the disease onset [182]. In contrast, pseudoatrophy occurs during the first 6–12 months after the administration of highly effective drugs [187,188] and after autologous hematopoietic stem cell transplantation [189], partly because of the resolution of inflammation and edema. Therefore, a re-assessment of brain volume is recommended after treatment initiation [190], particularly in studies or trials with neuroprotection as their main outcome. Another interesting structure with a potential for volumetric variations in response to inflammation is the hippocampus, where some studies have detected that hypertrophy of the dentate gyrus subfield is positively correlated with brain WM lesion volume [173]. Nevertheless, other studies have found early atrophy in this subfield [172,174], indicating the need for further investigation.

A similar atrophy rate of 0.47% volume loss per year has been reported in patients with NMOSD, with rates even higher in the GM of patients with long spinal cord lesions [191]. It is unclear whether brain atrophy is a primary diffuse or a secondary localized neurodegenerative phenomenon in NMOSD. In fact, both diffuse and regional atrophy in the optic and corticospinal tracts were detected in WM [94,192,193], whereas other studies found no evidence of WM atrophy [142]. Similarly, the presence of GM atrophy is controversial and not detected by all studies [119,142,194,195].

At the cortical level, cortical anomalies mainly limited to the visual [27,94,181,196] and sensorimotor cortices [94] have consistently been found, suggesting a mechanism of damage resulting from Wallerian degeneration from the optic nerve and spinal cord, independent of brain lesions [181]. Other investigations have reported the involvement of GM structures, such as the thalamus and hippocampus, especially in cognitively impaired individuals [27,173,192,197], although the abnormalities seem milder than in MS.

Atrophy distribution in the spinal cord supports the idea of a secondary neurodegenerative mechanism underlying the disease. In fact, spinal cord atrophy not only correlates with the number of prior myelitis cases [198] but also co-localizes with spinal cord lesions [91,199] and is not found in patients without history of myelitis [199]. Table 5 summarizes these findings, and examples of brain and spinal cord atrophy in patients with MS and NMOSD are shown in Figure 4.

CONCLUSIONS

The application of MRI, especially advanced techniques, has significantly enhanced our knowledge of MS and NMOSD. In MS, MRI studies highlighted the role of CSF and meningeal inflammation in the development and distribution of damage. Blood-brain barrier breakdown at the venular level is pulsed during the acute phases of the disease and leads to lesion formation, whose focal inflammation can resolve or become chronic in slowly expanding or chronic-active lesions. In addition to focal damage, MS pathology appears diffuse and involves normal-appearing tissues. Similarly, atrophy is diffuse and partially independent of lesions, suggesting a concomitant mechanism of primary and secondary neurodegeneration.

In NMOSD, summarizing the literature is more challenging, owing to inconsistencies among studies. However, only a few observations were made. Tissue damage appears to be localized within lesions or at sites subjected to secondary degenerative phenomena within the visual and sensorimotor systems. A diffuse increase in MD (with no evidence of axonal damage) has been reported in several studies and fits the hypothesis of chronic subtle damage to the blood-brain barrier. Damage to the blood-meningeal barrier may be another route of entry for AQP4-IgGs into the CNS. Finally, in contrast to MS, to date, there is no evidence of chronic-active inflammation in NMOSD, possibly explaining the lack of clinical secondary progression despite the severity of acute relapses.

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Conflicts of Interest

Laura Cacciaguerra received speaker and consultant honoraria from ACCMED, Roche, BMS Celgene, and Sanofi. Maria A. Rocca received consulting fees from Biogen, Bristol Myers Squibb, Eli Lilly, Janssen, Roche, and speaker honoraria from AstraZaneca, Biogen, Bristol Myers Squibb, Bromatech, Celgene, Genzyme, Horizon Therapeutics Italy, Merck Serono SpA, Novartis, Roche, Sanofi and Teva, she receives research support from the MS Society of Canada, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla. She is Associate Editor for *Multiple Sclerosis and Related Disorders*.

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Author Contributions

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