

A case-based narrative review of the diagnostic approach to central nervous system demyelinating disorders

Uma revisão narrativa baseada em casos clínicos sobre a abordagem diagnóstica dos principais distúrbios desmielinizantes do sistema nervoso central

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ABSTRACT

Central nervous system demyelinating disorders (CNS-DD) can cause abrupt, disabling, yet potentially reversible neurologic deficits; rapid recognition is essential because acute immunotherapy is time-sensitive. This narrative review, anchored in a three-patient case series, outlines a practical diagnostic workflow to differentiate the main inflammatory demyelinating syndromes. We describe: (1) multiple sclerosis in a 23-year-old man with optic neuritis, typical brain MRI lesions, and cerebrospinal fluid oligoclonal bands fulfilling McDonald criteria; (2) aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder in a 24-year-old woman with longitudinally extensive myelitis, optic symptoms, and area postrema syndrome; and (3) MOG antibody-associated disease in a 23-year-old postpartum woman with ADEM-like encephalopathy and strongly positive serum MOG-IgG. Across entities, lesion topography on brain/spine MRI, CSF profile, and serum antibody testing (AQP4-IgG, MOG-IgG) are pivotal to exclude mimics and guide early treatment.

Keywords: Demyelinating Diseases; Central Nervous System; Multiple Sclerosis; Neuromyelitis Optica; Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

RESUMO

As doenças desmielinizantes do sistema nervoso central (DD-SNC) podem causar déficits neurológicos de início abrupto, incapacitantes, porém potencialmente reversíveis; seu reconhecimento rápido é essencial, uma vez que a imunoterapia na fase aguda é tempo-dependente. Esta revisão narrativa, fundamentada em uma série de três casos clínicos, apresenta uma abordagem diagnóstica prática para diferenciar as principais síndromes desmielinizantes inflamatórias. Descrevemos: (1) esclerose múltipla em um homem de 23 anos com neurite óptica, lesões encefálicas típicas à ressonância magnética e bandas oligoclonais no líquido cefalorraquidiano, preenchendo os critérios de McDonald; (2) doença do espectro da neuromielite óptica com AQP4-IgG positivo em uma mulher de 24 anos com mielite longitudinalmente extensa, sintomas ópticos e síndrome da área postrema; e (3) doença associada ao anticorpo anti-MOG (MOGAD) em uma mulher de 23 anos no período pós-parto, apresentando encefalopatia semelhante à ADEM e MOG-IgG sérico fortemente positivo. Entre essas diferentes entidades, a topografia das lesões na ressonância magnética de encéfalo e medula espinhal, o perfil do líquido cefalorraquidiano e a pesquisa de anticorpos séricos (AQP4-IgG e MOG-IgG) são fundamentais para excluir diagnósticos diferenciais e orientar o tratamento precoce.

Palavras-chave: Doenças Desmielinizantes; Sistema Nervoso Central; Esclerose Múltipla; Neuromielite Óptica; Doença Associada a Anticorpos contra a Glicoproteína de Oligodendrócitos da Mielina

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INTRODUCTION

Central nervous system demyelinating disorders (CNS-DD) are inflammatory autoimmune diseases that damage the central nervous system (CNS) white matter myelin and cause acute disabling symptoms, often reversible. Because treatment is time-sensitive, early diagnosis is crucial¹. This narrative review, illustrated by a three-case series, presents a practical approach to the diagnostic algorithm for these conditions.

METHODS

Literature review

A focused and iterative narrative review was conducted to summarize the clinical presentation, diagnostic evaluation, and principal distinguishing features of multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and MOG antibody-associated disease (MOGAD). Separate searches were performed in PubMed/MEDLINE and Embase for each disorder, with emphasis on diagnostic criteria, differential diagnosis, neuroimaging, cerebrospinal fluid findings, and disease-specific antibody testing.

To obtain a focused and clinically relevant evidence base, the principal searches prioritized narrative and systematic reviews, clinical guidelines, consensus statements, recommendation papers, and original studies proposing or validating diagnostic criteria. Editorials, letters, comments, conference abstracts or proceedings, and other non-full-length publication types were excluded when applicable.

These searches were complemented by targeted searches on biomarkers, specific differential diagnoses, and therapeutic implications. Earlier landmark studies and additional topic-specific references were identified through backward citation tracking of selected diagnostic criteria, guidelines, consensus statements, and reviews. These supplementary searches were purposive rather than exhaustive and supported topics not fully covered by the principal diagnostic strategy.

The principal database searches identified 399 records. After removal of 108 duplicates, 291 underwent title screening, 151 were retained for abstract review, and 63 were assessed in full text. Fifteen publications were included in the core diagnostic evidence set supporting the comparative discussion of MS, NMOSD, and MOGAD.

Further 30 publications were identified through targeted searches and backward citation tracking, mostly addressed topics not fully captured by the principal diagnostic strategy, including pathophysiology, epidemiology, biomarkers and specific differential diagnoses. Of the resulting 45 candidate publications, 40 were included in the final narrative review.

Case selection and clinical data collection

The review was illustrated by three real clinical cases managed in the Internal Medicine wards of Hospital Universitário Pedro Ernesto during the study period. Cases were selected through convenience and purposive sampling because they represented three major inflammatory CNS-DD and provided complementary examples of the diagnostic reasoning required to distinguish these disorders.

Only patients initially admitted and managed under Internal Medicine service and subsequent co-managed with the Neurology department were included. This selection was intentional, as the case series was designed to emphasize the role of general physicians in the early recognition, initial investigation, stabilization, and timely referral of patients presenting with potentially CNS-DD. Neurological consultation was obtained in all cases and guided diagnostic confirmation and treatment. Before discharge, follow-up with the institutional Neuroimmunology outpatient service was arranged jointly by both teams.

The complete medical records of the index hospitalization and one-year follow-up period of all patients were retrospectively reviewed by the first author. Data collected included demographic characteristics, medical history, neurological findings, laboratory and cerebrospinal fluid results, neuroimaging, antibody testing, treatments, clinical course, discharge status and one-year outcomes. Events occurring beyond this period were not assessed.

Diagnostic tests were performed as part of routine care. Cerebrospinal fluid analysis, AQP4-IgG and MOG-IgG testing, and other etiological investigations were obtained as early as feasible and, in all selected cases, before corticosteroids, plasma exchange, immunosuppressive therapy, or any other disease-specific treatment. Results were extracted from the original records and reports.

For didactic clarity, the cases were incorporated into the corresponding disease-specific sections rather than presented separately. Patient-specific information appears in *italics* within the narrative review, clearly distinguishing original clinical data from literature-derived information.

Data confidentiality and reporting

Clinical information was extracted and analyzed in a de-identified manner. Direct identifiers and nonessential potentially identifying details were omitted or generalized. The cases were reported in accordance with CARE guideline.

Use of artificial intelligence-assisted technologies

ChatGPT (OpenAI) was used solely for language editing and table formatting. No literature searches, data collection, data analysis, evidence selection, figures or

scientific content generation were performed using artificial intelligence. All authors reviewed and approved the final manuscript and assume full responsibility for its content.

Ethical considerations

The study was approved by Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro Research Ethics Committee (approval number: 8.425.125; CAAE: 97943626.0.0000.5259). Written informed consent for participation was obtained from each patient. All data were handled in accordance with the Declaration of Helsinki.

Overview

Most CNS-DD present abruptly, peak within hours to days, and remit over weeks. Lesions are initially focal, often involving the optic nerve, brainstem, cerebellar pathways, and/or spinal cord, but may become multifocal over time. Systemic symptoms are uncommon and should prompt evaluation for alternative diagnoses (e.g., infection, malignancy, paraneoplastic syndromes)².

The diagnostic workup should begin by confirming demyelination and characterizing the magnetic resonance imaging (MRI) pattern on brain and neuroaxis imaging³⁻⁵. Cerebrospinal fluid (CSF) analysis is recommended in most suspected cases and should ideally be obtained before treatment to minimize false-negative results.

Differential diagnosis

The differential diagnosis of CNS-DD should be guided by the temporal profile, predominant neurological syndrome, MRI lesion distribution, cerebrospinal fluid findings, and associated systemic manifestations. Encephalopathy, meningeal symptoms, marked pleocytosis, hypoglycorrhachia, fever, or constitutional features suggest infectious, granulomatous, or systemic autoimmune disorders, whereas hyperacute onset, diffusion restriction, hemorrhage, or vascular-territory lesions favor vascular causes.

Progressive myelopathy with cord compression, perimedullary flow voids, symmetric tract involvement, metabolic risk factors, mass-like, persistently enhancing lesions, steroid dependence or progressive deterioration may indicate structural, vascular, nutritional, hereditary or neoplastic etiologies. Key distinguishing features of these conditions are summarized in **Supplementary Data – TABLE S1**.

Therapeutic implications

Although a comprehensive discussion of treatment is beyond the scope of this review, acute attacks are generally managed with high-dose intravenous

TABLE 1 – Comparative main features of MS, NMOSD, and MOGAD

Feature	Multiple sclerosis	NMOSD	MOGAD
Typical demographic pattern	Young adults; female predominance, but either sex	Marked female predominance; often associated with systemic autoimmunity	Children and adults; no strong overall sex predominance
Common attacks	Unilateral optic neuritis; partial myelitis; focal brainstem/cerebellar or supratentorial syndrome	Severe optic neuritis; longitudinally extensive myelitis; area postrema, brainstem, diencephalic, or cerebral syndrome	Optic neuritis; myelitis; ADEM; brainstem/cerebellar syndrome; cortical encephalitis
Optic nerve pattern	Usually unilateral, shorter-segment, anterior or retrobulbar	Often severe, bilateral or sequential; posterior pathway/chiasm may be involved	Often bilateral or longitudinally extensive; anterior involvement, disc edema, and perineural enhancement are common
Spinal cord pattern	Usually short-segment and peripheral	Usually longitudinally extensive and central; cord swelling may occur	Long lesions are common; conus and central gray matter H-sign favor MOGAD
Brain MRI	Ovoid periventricular, cortical/juxtacortical, infratentorial lesions; CVS and PRL can support diagnosis	Area postrema, hypothalamic/diencephalic, brainstem, and heterogeneous corpus callosum lesions	Poorly demarcated ADEM-like lesions, deep gray matter or cortical involvement; lesions may resolve substantially
CSF	CSF-restricted oligoclonal bands common; kFLC may substitute in the 2024 criteria	OCB uncommon; pleocytosis and elevated protein may occur during attacks	OCB uncommon but possible; pleocytosis is frequent in acute attacks
Disease-defining antibody	None	Serum AQP4-IgG	Serum MOG-IgG
Course	Relapsing, progressive, or selected radiologically isolated presentations	Usually relapsing; disability accumulates from attacks	Monophasic or relapsing; recurrent optic neuritis is common among relapsing phenotypes
Practical diagnostic caution	Do not apply MS criteria to atypical syndromes or nonspecific MRI lesions	A positive AQP4-IgG requires a compatible core syndrome and exclusion of a better diagnosis	Interpret low-positive MOG-IgG only in a compatible phenotype with supporting features

Caption: ADEM, acute disseminated encephalomyelitis; AQP4-IgG, aquaporin-4 immunoglobulin G; CSF, cerebrospinal fluid; CVS, central vein sign; kFLC, kappa free light chains; MOGAD, MOG antibody-associated disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; OCB, oligoclonal bands; PRL, paramagnetic rim lesion.

corticosteroids, with plasma exchange therapy reserved for severe or refractory cases. Subsequent treatment differs among disorders: MS requires individualized disease-modifying and NMOSD generally requires relapse-prevention therapy. In MOGAD, maintenance immunotherapy is individualized and usually reserved for patients with relapsing course or substantial disability risk⁶⁻⁸.

Timely recognition and accurate differentiation are therefore essential, as delays may postpone rescue therapy and misclassification may lead to inappropriate long-term treatment, particularly in NMOSD and relapsing MOGAD, in which recurrent attacks may result in substantial and sometimes irreversible disability^{7,8}. Further treatment details are available on **Supplementary Data – TABLE S2**.

Multiple sclerosis (MS)

A previously healthy 23-year-old man was admitted with a one-week history of painless horizontal

binocular diplopia. He reported prior lower-limb and anterior thoracic paresthesias that resolved spontaneously within two weeks.

MS is the most prevalent chronic inflammatory demyelinating disease of the CNS. Its biology involves adaptive and innate immune mechanisms, including T cells, B cells, and activated microglia⁹⁻¹¹. It typically begins in early adulthood, is more common in women and white individuals (although it may follow a more severe course in non-white populations), and most often presents as a relapsing-remitting phenotype.

Most patients have evidence of prior Epstein-Barr virus infection, supporting a possible, although not yet fully established, causal relationship¹². Vitamin D deficiency¹³ and smoking¹⁴ are well-established risk factors, whereas childhood or adolescent obesity¹⁵ and intestinal dysbiosis¹⁶ remain under investigation.

Clinical presentation is variable, but typical attacks normally include unilateral optic neuritis, partial myelitis, focal supratentorial syndromes, and focal brainstem or cerebellar syndromes lasting more than 24 hours¹⁷. Features that should prompt reconsideration of the diagnosis include a hyperacute onset, complete or bilateral visual loss with poor recovery, longitudinally extensive myelitis, prominent systemic inflammation, multiple cranial neuropathies, meningismus, or symptoms that cannot be localized to a focal CNS lesion¹⁸.

Although male, our patient had clinical features suggestive of MS; he was eutrophic, reported childhood infectious mononucleosis, and had low vitamin D levels. MRI showed multiple ovoid T2/FLAIR-hyperintense lesions in periventricular, juxtacortical, callosal, and infratentorial regions, some with T1 black holes, and CSF analysis was positive for oligoclonal bands (OCB).

MS was traditionally diagnosed according to the 2017 McDonald criteria¹⁹, which required evidence of dissemination in space and time. The 2024 revision, published in 2025, substantially expanded this framework³ (FIGURE 1). Dissemination in space continues to rely on the presence of typical lesions affecting at least two distinct CNS regions, but the optic nerve is now recognized as a fifth anatomical location. Optic nerve involvement may be demonstrated by MRI or by optical coherence tomography or visual evoked potentials, the latter two of which were not recognized in the 2017 criteria.

As in the last criteria, evidence of dissemination in time may still be substituted by evidence of intrathecal immune activity, demonstrated by either CSF-restricted oligoclonal bands or an elevated kappa free light-chain index; however, the 2024 revision also introduced an additional pathway in selected clinical settings, allowing dissemination in time to be waived when at least four of the five typical anatomical locations are involved.

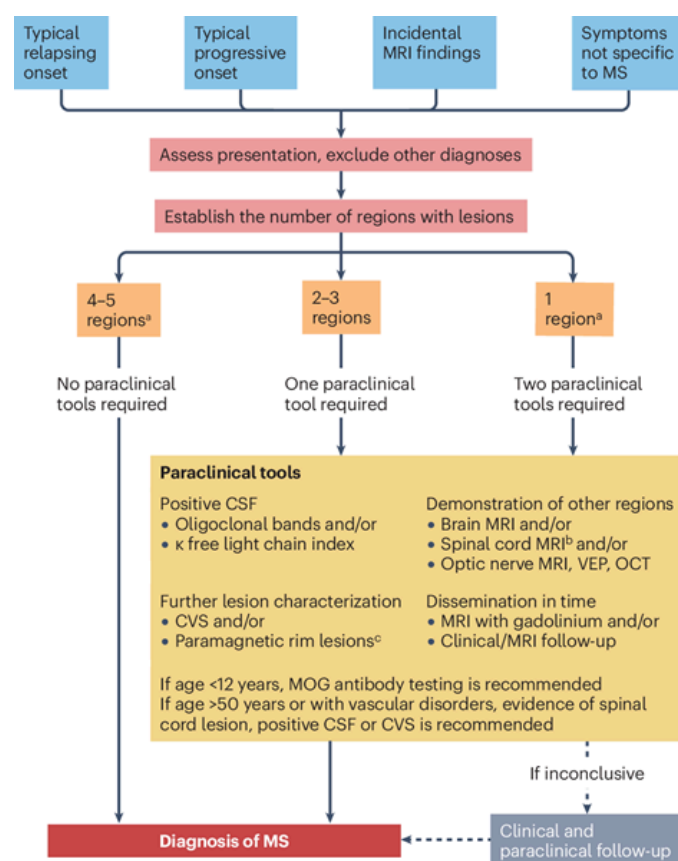


FIGURE 1 – 2024 McDonald criteria for MS

Source: 2024 McDonald criteria²⁰

Caption: CSF, cerebrospinal fluid; CVS, central vein sign; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCT, optical coherence tomography; VEP, visual evoked potentials.

Careful evaluation and exclusion of alternative diagnoses, including other CNS demyelinating disorders, vascular diseases, and compressive spinal cord lesions, are still strongly recommended and should always be evaluated, specially when oligoclonal bands are absent.

On MRI, MS lesions classically predominate in the periventricular white matter and frequently appear as ovoid lesions oriented perpendicular to the lateral ventricles, known as Dawson's fingers²¹. Susceptibility-sensitive MRI sequences may demonstrate a small vein coursing centrally through white matter lesions, the central vein sign, which improves diagnostic specificity²². Paramagnetic rim lesions are also strongly associated with MS and reflect chronic active inflammation at the lesion edge²³. Both findings were incorporated into selected diagnostic pathways in the revised criteria as markers that increase diagnostic specificity. The updated framework also permits the diagnosis of MS in selected individuals without a previous typical clinical attack, including some radiologically isolated presentations, when the required combinations of lesion distribution and supportive biomarkers are present.

Conversely, findings such as predominantly symmetric lesions, meningeal enhancement, superficial siderosis, poorly defined or crescent-shaped lesions, hemorrhage, infarction, longitudinally extensive spinal cord lesions, or relative preservation of the U-fibers are atypical for MS and should redirect the diagnostic investigation toward alternative etiologies²⁴.

Serum glial fibrillary acidic protein is a promising biomarker for prognostic assessment and disease monitoring, although its routine clinical use remains limited by availability and the lack of standardized thresholds²⁵.

He was diagnosed with highly active relapsing-remitting MS, achieved complete symptom resolution within one week after methylprednisolone, and started natalizumab after discharge; at one-year follow-up, he had no relapses or sequelae.

Our patient showed the classic relapse-and-remission pattern, consistent with a relapsing-remitting phenotype. However, MS can present with other variants or progress to them, to name some¹⁸:

- **Primary progressive form:** symptom progression for ≥ 1 year without remissions.
- **Secondary progressive form:** similar to primary progressive form but preceded by a relapsing phase.
- **Radiologically isolated syndrome:** MRI MS lesions detected incidentally.

Neuromyelitis optica spectrum disorders (NMOSD)

A 24-year-old woman with juvenile idiopathic arthritis in long-term remission presented with acute quadriplegia, hyperreflexia, spasticity, and spontaneous nystagmus (2 weeks), later complicated by pulmonary septic shock requiring invasive support. She had prior bilateral visual blurring and myelopathic symptoms (T8 sensory level, Lhermitte's sign, Uhthoff's phenomenon) plus area postrema syndrome.

Neuromyelitis optica spectrum disorders (NMOSD), formerly known Devic syndrome, were long considered a variant of MS. Their pathogenesis involves a complement-mediated autoimmune astrocytopathy triggered by antibodies against aquaporin-4 (AQP4-IgG), expressed on astrocytic endfeet in the brain, spinal cord, and optic chiasm, leading to blood-brain barrier disruption, oligodendrocyte injury, neuronal death, and synaptic dysfunction²⁶.

It more often affects asian and afro-descendant individuals, is nine times more common in women, and typically begins around age 40. It is frequently associated with autoimmune disease, particularly connective tissue diseases²⁷. Without treatment, up to 98% develop disabling cumulative relapses²⁸.

NMOSD typically presents with optic neuritis, longitudinally extensive transverse myelitis (LETM), and/or area postrema syndrome, but may involve brainstem, cerebral, and diencephalic syndromes, myeloradiculopathy,

uveitis, and neuropsychiatric features⁴. Lhermitte's sign and Uhthoff's phenomenon although classically associated with MS, simply indicate demyelination and don't reliably distinguish among CNS-DD²⁹.

CSF was normal, limb electromyoneurography supported diffuse demyelination, and MRI revealed inflammatory demyelinating lesions in the brainstem, occipital corpus callosum, and throughout the spinal cord. Serum AQP4-IgG was positive, while CSF OCB and antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) were negative.

NMOSD is diagnosed using the 2015 criteria⁴: AQP4-IgG seropositivity with almost any demyelination is confirmatory. In seronegative patients, differentiation from MS is harder and requires stricter criteria (FIGURE 2); In these cases, MOG-IgG testing is essential to distinguish NMOSD from myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)³⁰.

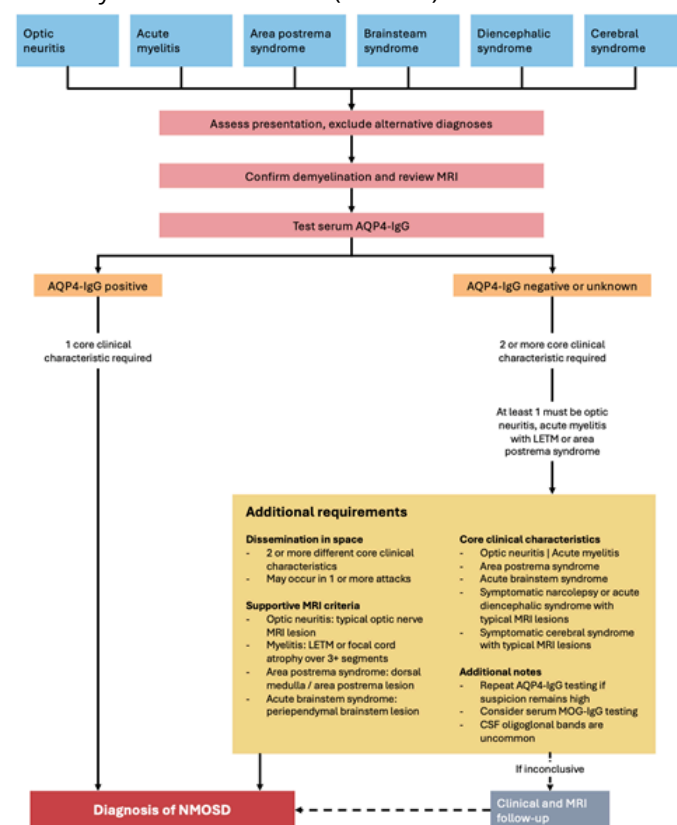


FIGURE 2 – Diagnostic flowchart for NMOSD

Source: adapted from NMOSD 2015 diagnostic criteria⁴ and inspired by the 2024 McDonald criteria flowchart²⁰

Caption: AQP4-IgG, aquaporin-4 immunoglobulin G; CSF, cerebrospinal fluid; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder.

AQP4-IgG is mainly produced extrathecaally, so serum testing is preferred. Titers and serostatus do not correlate with severity or course, therefore serial monitoring is not recommended. Over 75% of patients are seropositive; seronegative cases are more often male, white, younger, and less visually affected^{26,31}. Neurofilament light chain³² and serum/CSF GFAP³³ are promising biomarkers.

Typical findings include LETM, bilateral extensive optic neuritis, chiasmal involvement, area postrema lesions, and heterogeneous "cloud-like" corpus callosum lesions³⁴; specific imaging criteria can help distinguish NMOSD from MS³⁴.

Hyperacute (< 4 hours) or chronic (> 4 weeks) presentations are rare; MRI lesions rarely persist > 3 months, and CSF OCB are uncommon. Before diagnosis, systemic inflammatory diseases, MOGAD, spondylotic myelopathy, ischemia, nutritional deficiencies, neoplasms and hereditary neuropathies should be excluded²⁶.

After stabilization and NMOSD confirmation, corticosteroids plus azathioprine were started. She was discharged after two months with lower-limb paraplegia, reduced visual acuity, and neurogenic bladder, but had no relapses at one-year follow-up.

Each NMOSD relapse can be viewed as an "neuroimmunologic stroke", often leaving severe, poorly reversible deficits; however a minority of sequelae arise from the initial attack, and modern therapies have reduced their overall frequency³⁵.

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

A 23-year-old woman with preeclampsia developed confusion and subacute left arm weakness in the third postpartum week, progressing within the next day with left hemiplegia, right facial deviation, and sphincter release. CT angiography showed nonspecific changes but no vascular occlusion. She was confused and obtunded.

MOGAD is a rare, typically monophasic CNS-DD, often triggered by viral infections and, less commonly, vaccination, with no sex predilection and mean onset at age 30. It presents mainly with optic neuritis, LETM, acute disseminated encephalomyelitis (ADEM), or cortical encephalitis; relapses are uncommon (often with optic neuritis) and seroconversion is a potential protective factor or predictor for relapses³⁰.

MOGAD is mediated by MOG-IgG, triggering complement activation with T- and B-cell involvement and neutrophilic/eosinophilic inflammation, leading to astrocytopathy, demyelination, axonal injury, and blood-brain barrier disruption; oligodendrocyte cytoskeletal changes may also contribute via unclear mechanisms³⁶.

Pregnancy, particularly the third trimester, increases overall CNS-DD risk, especially NMOSD, possibly due to increased placental AQP4 expression; links with MOGAD and other CNS-DD are hypothesized but still uncertain³⁷.

Headache, visual prodromes, optic disc edema and hemorrhage, and extensive segmental lesions favor MOGAD over other CNS-DD; conversely, area postrema syndrome is very rare³⁸.

MRI showed extensive cerebral demyelinating lesions with right-sided mass effect, consistent with ADEM; CSF was

negative for infection but positive for OCB.

ADEM is an rare, usually monophasic multifocal CNS-DD that may be primary or secondary to other CNS-DD; it predominantly affects children and follows viral infection (or rarely vaccination). It presents with acute encephalopathy and multifocal deficits, with MRI showing reversible, poorly defined demyelinating white-matter lesions (often involving thalami and basal ganglia). CSF may show mild pleocytosis and elevated protein, usually without CSF OCB³⁹.

Given the lack of preceding infection/vaccination, atypical age for primary ADEM, and positive CSF OCB, we extended the etiologic workup: AQP4-IgG was negative, while serum MOG-IgG was strongly positive.

MOGAD diagnosis follows the 2023 criteria⁵, primarily based on serum MOG-IgG; CSF MOG-IgG testing help in selected cases (FIGURE 3). MRI features favoring MOGAD include long-segment optic nerve involvement with chiasm/tract sparing, perioptic enhancement, deep gray matter (especially thalamic) signal changes, pontine lesions, conus involvement and an axial "H-sign"⁴⁰.

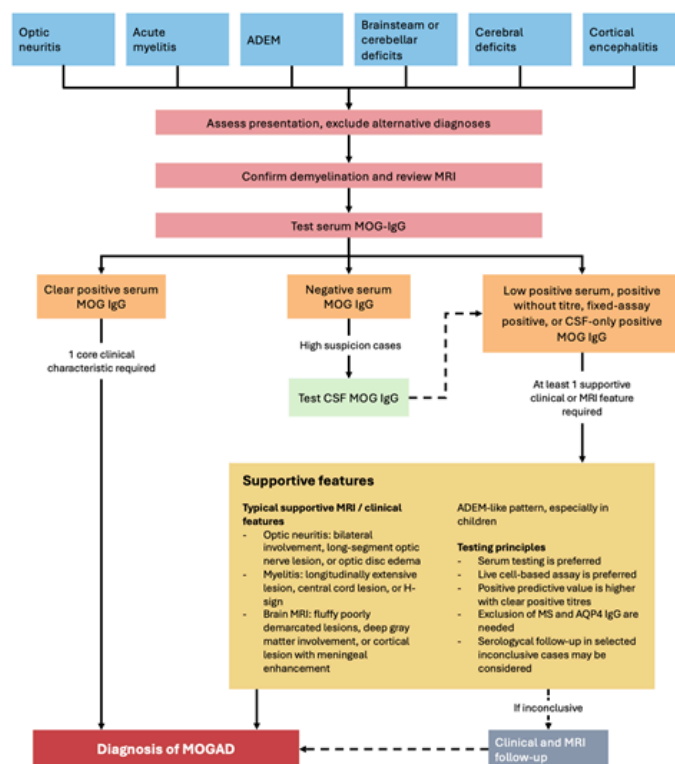


FIGURE 3 – Diagnostic flowchart for MOGAD

Source: adapted from MOGAD 2023 diagnostic criteria⁵ and inspired by the new McDonald criteria flowchart²⁰

Caption: ADEM, acute disseminated encephalomyelitis; AQP4-IgG, aquaporin-4 immunoglobulin G; CSF, cerebrospinal fluid; MOGAD, MOG antibody-associated disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

She was diagnosed with MOGAD and improved after methylprednisolone but had mild residual confusion and hemiparesis, so six plasma exchange sessions were added; she was discharged without sequelae and remained asymptomatic at one-year follow-up.

CONCLUSION

In this article, we reviewed the diagnostic approach to MS, NMOSD, and MOGAD through three illustrative cases. By integrating clinical presentation, MRI patterns, cerebrospinal fluid findings, and antibody testing, these cases highlight both the overlap among CNS-DD and the key features that support their differentiation. The main clinical, diagnostic, therapeutic, and outcome data from the three cases are summarized in TABLE 2.

TABLE 2 – Clinical characteristics, diagnostic findings, treatment, and outcomes of the three illustrative cases

Variable	Case 1 - MS	Case 2 - NMOSD	Case 3 - MOGAD
Age	23 years	24 years	23 years
Sex	Male	Female	Female
Clinical Characteristics	Painless horizontal binocular diplopia with prior transient lower-limb and thoracic paresthesias	Acute quadriplegia, hyperreflexia, spasticity, nystagmus, prior bilateral visual blurring, myelopathic symptoms, and area postrema syndrome	Postpartum encephalopathy with rapidly progressive left hemiplegia, right facial deviation, and sphincter release
MRI findings	Multifocal demyelinating lesions in the periventricular and juxtacortical white matter, corpus callosum, brainstem, and cerebellar peduncles. Mildly elevated protein and CSF-restricted oligoclonal bands; otherwise unremarkable.	Inflammatory demyelinating lesions in the brainstem, occipital corpus callosum, and extensive regions of the spinal cord.	Extensive cerebral demyelinating lesions with right-sided mass effect (ADEM-like).
CSF findings	Mildly elevated protein and CSF-restricted oligoclonal bands; otherwise unremarkable.	Mildly elevated protein and absent oligoclonal bands; otherwise unremarkable.	CSF-restricted oligoclonal bands; otherwise unremarkable.
Antibody testing	Serum AQP4-IgG and MOG-IgG negative.	Serum AQP4-IgG positive and MOG-IgG negative.	Serum MOG-IgG strongly positive and AQP4-IgG negative.
Treatment	IV methylprednisolone for the acute attack, followed by natalizumab	IV methylprednisolone for the acute attack, followed by azathioprine.	IV methylprednisolone followed by six plasma-exchange sessions. No maintenance therapy after corticosteroid tapering.
Outcome	Complete symptom resolution within one week; no relapses or neurological sequelae at one-year follow-up.	Discharged after two months with lower-limb paraplegia, reduced visual acuity, and neurogenic bladder; no further relapses at one-year follow-up.	Discharged without neurological sequelae and remained asymptomatic at one-year follow-up.

Caption: ADEM, acute disseminated encephalomyelitis; AQP4-IgG, aquaporin-4 immunoglobulin G; CSF, cerebrospinal fluid; IV, intravenous; MOGAD, MOG antibody-associated disease; MOG-IgG, myelin oligodendrocyte glycoprotein immunoglobulin G; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

Accurate classification of CNS-DD requires integrating the temporal profile, lesion distribution, laboratory findings, and diagnostic red flags. Early recognition and exclusion of major mimics are essential to enable timely specialist assessment, appropriate disease-specific treatment, and prevention of irreversible disability.

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REFERENCES

- Coutinho Costa VG, Araújo SES, Alves-Leon SV, Gomes FCA. Central nervous system demyelinating diseases: glial cells at the hub of pathology. *Front Immunol*. 2023 May 16;14:1135540. doi:10.3389/fimmu.2023.1135540
- Filippi M, Preziosa P, Margoni M, Rocca MA. Diagnostic Criteria for Multiple Sclerosis, Neuromyelitis Optica Spectrum Disorders, and Myelin Oligodendrocyte Glycoprotein-immunoglobulin G-associated Disease. *Neuroimaging Clinics of North America*. 2024 Aug;34(3):293–316. doi:10.1016/j.nic.2024.03.001
- Montalban X, Lebrun-Frény C, Oh J, Arrambide G, Moccia M, Pia Amato M, et al. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria. *The Lancet Neurology*. 2025 Oct;24(10):850–65. doi:10.1016/S1474-4422(25)00270-4
- Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015 Jul 14;85(2):177–89. doi:10.1212/WNL.0000000000001729
- Banwell B, Bennett JL, Marignier R, Kim HJ, Brilot F, Flanagan EP, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. *The Lancet Neurology*. 2023 Mar;22(3):268–82. doi:10.1016/S1474-4422(22)00431-8
- Rashid W, Ciccarelli O, Leary SM, Arun T, Doshi A, Evangelou N, et al. Using disease-modifying treatments in multiple sclerosis: Association of British Neurologists (ABN) 2024 guidance. *Pract Neurol*. 2025 Feb;25(1):18–24. doi:10.1136/pn-2024-004228
- Kümpfel T, Gighlhuber K, Aktas O, Ayzenberg I, Bellmann-Strobl J, Häußler V, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) – revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: Attack therapy and long-term management. *J Neurol*. 2024 Jan;271(1):141–76. doi:10.1007/s00415-023-11910-z
- Carnero Contentti E, Correale J, Rojas JJ, Alonso R, Becker J, Caparó Zamalloa C, et al. Latin American RAND/UCLA modified Delphi consensus recommendations for management and treatment of adult MOGAD patients in clinical practice. *Multiple Sclerosis and Related Disorders*. 2025 Jul;99:106460. doi:10.1016/j.msard.2025.106460
- Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. *Nat Rev Immunol*. 2015 Sep;15(9):545–58. doi:10.1038/nri3871
- Comi G, Bar-Or A, Lassmann H, Uccelli A, Hartung H, Montalban X, et al. Role of B Cells in Multiple Sclerosis and Related Disorders. *Annals of Neurology*. 2021 Jan;89(1):13–23. doi:10.1002/ana.25927
- Geladaris A, Häusler D, Weber MS. Microglia: The Missing Link to Decipher and Therapeutically Control MS Progression? *IJMS*. 2021 Mar 27;22(7):3461. doi:10.3390/ijms22073461
- Bjornevik K, Cortese M, Healy BC, Kuhle J, Mina MJ, Leng Y, et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. *Science*. 2022 Jan 21;375(6578):296–301. doi:10.1126/science.abj8222
- Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-Hydroxyvitamin D Levels and Risk of Multiple Sclerosis. *JAMA*. 2006 Dec 20;296(23):2832. doi:10.1001/jama.296.23.2832

14. Ramanujam R, Hedström AK, Manouchehrinia A, Alfredsson L, Olsson T, Bottai M, et al. Effect of Smoking Cessation on Multiple Sclerosis Prognosis. *JAMA Neurol.* 2015 Oct 1;72(10):1117. doi:10.1001/jamaneurol.2015.1788
15. Liu Z, Zhang TT, Yu J, Liu YL, Qi SF, Zhao JJ, et al. Excess Body Weight during Childhood and Adolescence Is Associated with the Risk of Multiple Sclerosis: A Meta-Analysis. *Neuroepidemiology.* 2016;47(2):103–8. doi:10.1159/000450854
16. Dopkins N, Nagarkatti PS, Nagarkatti M. The role of gut microbiome and associated metabolome in the regulation of neuroinflammation in multiple sclerosis and its implications in attenuating chronic inflammation in other inflammatory and autoimmune disorders. *Immunology.* 2018 Jun;154(2):178–85. doi:10.1111/imm.12903
17. Oh J. Diagnosis of Multiple Sclerosis. *CONTINUUM: Lifelong Learning in Neurology.* 2022 Aug;28(4):1006–24. doi:10.1212/CON.0000000000001156
18. Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: progress and challenges. *The Lancet.* 2017 Apr;389(10076):1336–46. doi:10.1016/S0140-6736(16)30959-X
19. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology.* 2018 Feb;17(2):162–73. doi:10.1016/S1474-4422(17)30470-2
20. Moccia M, Ciccarelli O, Thompson A. Implementation of the 2024 revision of the McDonald criteria for multiple sclerosis. *Nat Rev Neurol.* 2025 Dec;21(12):664–6. doi:10.1038/s41582-025-01141-3
21. Wildner P, Stasiolek M, Matysiak M. Differential diagnosis of multiple sclerosis and other inflammatory CNS diseases. *Multiple Sclerosis and Related Disorders.* 2020 Jan;37:101452. doi:10.1016/j.msard.2019.101452
22. on behalf of the NAIMS Cooperative, Sati P, Oh J, Constable RT, Evangelou N, Guttmann CRG, et al. The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. *Nat Rev Neurol.* 2016 Dec;12(12):714–22. doi:10.1038/nrneurol.2016.166
23. Maggi P, Absinta M. Emerging MRI biomarkers for the diagnosis of multiple sclerosis. *Mult Scler.* 2024 Dec;30(14):1704–13. doi:10.1177/13524585241293579
24. Chen JJ, Carletti F, Young V, McKean D, Quaghebeur G. MRI differential diagnosis of suspected multiple sclerosis. *Clinical Radiology.* 2016 Sep;71(9):815–27. doi:10.1016/j.crad.2016.05.010
25. Sun M, Liu N, Xie Q, Li X, Sun J, Wang H, et al. A candidate biomarker of glial fibrillary acidic protein in CSF and blood in differentiating multiple sclerosis and its subtypes: A systematic review and meta-analysis. *Multiple Sclerosis and Related Disorders.* 2021 Jun;51:102870. doi:10.1016/j.msard.2021.102870
26. Jarius S, Aktas O, Azyenberg I, Bellmann-Strobl J, Berthele A, Giglhuber K, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) – revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part I: Diagnosis and differential diagnosis. *J Neurol.* 2023 Jul;270(7):3341–68. doi:10.1007/s00415-023-11634-0
27. Cruz RA, Chaudhary S, Guevara M, Meltzer E. Neuromyelitis Optica Spectrum Disorders (NMOSD) and Connective Tissue Disease (CTD): an Update for the Rheumatologist. *Curr Rheumatol Rep.* 2021 Jun;23(6):33. doi:10.1007/s11926-021-01000-2
28. Pandit L, D'Cunha A, Malapur PU. Incidence and Prevalence of Neuromyelitis Optica Spectrum Disorders in the Background of International Consensus Diagnostic Criteria – A Systematic Review. *Neurology India.* 2022 Sep;70(5):1771–9. doi:10.4103/0028-3886.359235
29. Park K, Tanaka K, Tanaka M. Uhthoff's Phenomenon in Multiple Sclerosis and Neuromyelitis Optica. *Eur Neurol.* 2014;72(3–4):153–6. doi:10.1159/000361045
30. Mewes D, Kuchling J, Schindler P, Khalil AAA, Jarius S, Paul F, et al. Diagnostik der Neuromyelitis-optica-Spektrum-Erkrankung (NMOSD) und der MOG-Antikörper-assoziierten Erkrankung (MOGAD). *Klin Monbl Augenheilkd.* 2022 Nov;239(11):1315–24. doi:10.1055/a-1918-1824
31. Carnero Contentti E, Rotstein D, Okuda DT, Paul F. How to avoid missing a diagnosis of neuromyelitis optica spectrum disorder. *Mult Scler.* 2025 Jan;31(1):8–22. doi:10.1177/13524585241292797
32. Barro C, Chitnis T, Weiner HL. Blood neurofilament light: a critical review of its application to neurologic disease. *Ann Clin Transl Neurol.* 2020 Dec;7(12):2508–23. doi:10.1002/acn3.51234
33. Ma X, Kermode AG, Hu X, Qiu W. Risk of relapse in patients with neuromyelitis optica spectrum disorder: Recognition and preventive strategy. *Multiple Sclerosis and Related Disorders.* 2020 Nov;46:102522. doi:10.1016/j.msard.2020.102522
34. Clarke L, Arnett S, Lilley K, Liao J, Bhuta S, Broadley SA. Magnetic resonance imaging in neuromyelitis optica spectrum disorder. *Clinical and Experimental Immunology.* 2021 Nov 2;206(3):251–65. doi:10.1111/cei.13630
35. Jiao Y, Fryer JP, Lennon VA, Jenkins SM, Quek AML, Smith CY, et al. Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica. *Neurology.* 2013 Oct;81(14):1197–204. doi:10.1212/WNL.0b013e3182a6cb5c
36. Takai Y, Misu T, Kaneko K, Chihara N, Narikawa K, Tsuchida S, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease: an immunopathological study. *Brain.* 2020 May 1;143(5):1431–46. doi:10.1093/brain/awaa102
37. Mao-Draayer Y, Thiel S, Mills EA, Chitnis T, Fabian M, Katz Sand I, et al. Neuromyelitis optica spectrum disorders and pregnancy: therapeutic considerations. *Nat Rev Neurol.* 2020 Mar;16(3):154–70. doi:10.1038/s41582-020-0313-y
38. Filippatou AG, Mukharesh L, Saidha S, Calabresi PA, Sotirchos ES. AQP4-IgG and MOG-IgG Related Optic Neuritis—Prevalence, Optical Coherence Tomography Findings, and Visual Outcomes: A Systematic Review and Meta-Analysis. *Front Neurol.* 2020 Oct 8;11:540156. doi:10.3389/fneur.2020.540156
39. Pohl D, Alper G, Van Haren K, Kornberg AJ, Lucchinetti CF, Tenenbaum S, et al. Acute disseminated encephalomyelitis: Updates on an inflammatory CNS syndrome. *Neurology.* 2016 Aug 30;87(9_Supplement_2). doi:10.1212/WNL.0000000000002825
40. Sechi E, Cacciaguerra L, Chen JJ, Mariotto S, Fadda G, Dinoto A, et al. Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD): A Review of Clinical and MRI Features, Diagnosis, and Management. *Front Neurol.* 2022 Jun 17;13:885218. doi:10.3389/fneur.2022.885218

Diagnosing MS, NMOSD, and MOGAD - Supplementary Data

TABLE S1 – Principal differential diagnoses of multiple sclerosis, AQP4-IgG-positive NMOSD, and MOGAD

Condition	Typical clinical clues	MRI, CSF, and confirmatory findings	Features favoring the alternative diagnosis
Acute disseminated encephalomyelitis (ADEM) ¹	Acute polyfocal neurologic syndrome, classically accompanied by encephalopathy, particularly in children; frequently follows an infection and is usually monophasic.	MRI typically shows large, bilateral, asymmetric, poorly demarcated T2/FLAIR lesions involving the subcortical and deep white matter, often with thalamic or basal-ganglia involvement. CSF may show mild pleocytosis or elevated protein; persistent CSF-restricted oligoclonal bands are uncommon.	Encephalopathy, simultaneous multifocal deficits, poorly defined lesions of similar age, and substantial lesion resolution on follow-up favor ADEM over MS. Serum MOG-IgG should be tested in ADEM-like presentations because this phenotype may represent MOGAD.
Autoimmune GFAP astrocytopathy ^{2,3}	Acute or subacute meningoencephalitis, encephalomyelitis, or myelitis, often with fever, headache, altered consciousness, tremor, ataxia, autonomic dysfunction, or optic-disc edema.	CSF commonly demonstrates lymphocytic pleocytosis and elevated protein. GFAP-IgG detection in CSF is more diagnostically specific than serum testing. Characteristic MRI findings include linear radial perivascular enhancement perpendicular to the ventricles, punctate enhancement, leptomeningeal involvement, and occasionally longitudinal spinal cord lesions.	A prominent meningeal or encephalitic syndrome, markedly inflammatory CSF, radial perivascular enhancement, and CSF GFAP-IgG favor GFAP astrocytopathy rather than MS, NMOSD, or MOGAD.
Neurosarcoidosis ⁴	Cranial neuropathies, chronic meningitis, hypothalamic-pituitary dysfunction, myelopathy, peripheral neuropathy, or multifocal CNS involvement; pulmonary, lymph-node, cutaneous, or ocular sarcoidosis may coexist.	MRI may show basilar or diffuse leptomeningeal enhancement, cranial-nerve enhancement, hypothalamic-pituitary lesions, or longitudinal spinal cord lesions with dorsal subpial enhancement. CSF frequently shows lymphocytic pleocytosis and elevated protein and may show hypoglycorrhachia. Probable disease requires compatible neurologic involvement and biopsy-proven systemic sarcoidosis; definite disease requires neural-tissue confirmation.	Persistent leptomeningeal or subpial enhancement, hypoglycorrhachia, multisystem sarcoidosis, and noncaseating granulomas favor neurosarcoidosis. Serum or CSF angiotensin-converting enzyme levels alone have insufficient diagnostic accuracy.
Neuro-Behçet disease ⁵	Neurologic disease in a patient with recurrent oral or genital ulceration, uveitis, skin lesions, or vascular manifestations. Parenchymal disease usually causes brainstem, pyramidal, cerebellar, or behavioral manifestations; nonparenchymal disease commonly presents with cerebral venous thrombosis or intracranial hypertension.	MRI frequently involves the brainstem, mesodiencephalic junction, thalamus, or basal ganglia. CSF may show neutrophilic or lymphocytic pleocytosis and elevated protein, whereas CSF-restricted oligoclonal bands are unusual. Diagnosis requires a compatible neurologic syndrome and established systemic Behçet disease after exclusion of alternative causes.	Mucocutaneous and ocular disease, venous thrombosis, brainstem-diencephalic lesion predominance, and inflammatory CSF without persistent oligoclonal bands favor Neuro-Behçet disease.
CLIPPERS ⁶	Subacute gait ataxia, diplopia, dysarthria, facial sensory symptoms, and other pontocerebellar manifestations, typically with a marked corticosteroid response and recurrence during rapid tapering.	MRI demonstrates numerous homogeneous punctate or curvilinear gadolinium-enhancing lesions, usually smaller than 3 mm, "peppering" the pons and cerebellar peduncles, without substantial mass effect. CSF findings are nonspecific. Biopsy may show predominantly perivascular CD4-positive T-cell inflammation.	The characteristic pontine enhancement pattern and corticosteroid responsiveness support CLIPPERS, but infection, lymphoma, vasculitis, sarcoidosis, and other inflammatory diseases must be rigorously excluded, particularly when lesions are large, necrotic, mass-like, or steroid-resistant.
Susac syndrome ⁷	Encephalopathy, headache, focal neurologic deficits, branch retinal artery occlusions, and sensorineural hearing loss. The complete clinical triad is frequently absent at initial presentation.	MRI classically shows central corpus-callosum lesions, including "snowball" lesions and later callosal holes; leptomeningeal enhancement may occur. Fluorescein angiography demonstrates branch retinal artery occlusions or arterial-wall hyperfluorescence, and audiometry typically confirms sensorineural hearing loss. CSF protein may be elevated, while oligoclonal bands are usually absent.	Central callosal lesions, retinal arterial occlusion, and cochlear hearing loss distinguish Susac syndrome from inflammatory demyelinating disease. Ophthalmologic and audiologic testing should be performed even when visual or auditory symptoms are not initially reported.

Sjögren syndrome with neurologic involvement ⁸	Sensory neuropathy, painful small-fiber neuropathy, cranial neuropathy, myelopathy, optic neuropathy, or encephalopathy. Neurologic manifestations may precede clinically evident sicca symptoms.	Brain lesions may resemble MS, and myelitis can be longitudinally extensive. Evaluation includes anti-SSA/Ro and anti-SSB/La antibodies, objective ocular and salivary tests, and minor salivary-gland biopsy when appropriate. CSF findings are variable.	Sicca symptoms, systemic autoimmunity, prominent peripheral neuropathy or sensory neuropathy, and confirmatory glandular testing support Sjögren syndrome. AQP4-IgG-positive optic neuritis or myelitis should generally be classified as coexisting NMOSD rather than attributed solely to Sjögren syndrome.
Neuropsychiatric systemic lupus erythematosus ⁹	Seizures, psychosis, cognitive dysfunction, headache, cerebrovascular disease, movement disorders, neuropathy, optic neuropathy, or myelitis in a patient with established or suspected systemic lupus erythematosus.	MRI may be normal or show nonspecific white-matter lesions, infarctions, hemorrhage, or, less commonly, inflammatory myelitis. CSF findings are nonspecific. Assessment should integrate systemic disease activity, complement levels, autoantibodies, vascular risk, infection screening, and medication-related causes.	Concurrent systemic lupus manifestations, cytopenias, hypocomplementemia, renal or cutaneous disease, and predominantly vascular or nonspecific MRI abnormalities favor neuropsychiatric lupus. AQP4-IgG should be tested in patients with optic neuritis or longitudinal myelitis.
Antiphospholipid syndrome ¹⁰	Arterial or venous thrombosis, recurrent pregnancy morbidity, stroke, transient ischemic attacks, cerebral venous thrombosis, seizures, migraine, or cognitive symptoms. Multifocal neurologic episodes may occasionally resemble MS.	MRI typically demonstrates ischemic lesions in arterial, lacunar, or watershed distributions rather than characteristic inflammatory demyelinating lesions. Diagnosis requires a qualifying clinical event and persistent lupus anticoagulant, anticardiolipin, or anti-β2-glycoprotein-I antibodies.	Previous thrombosis, pregnancy morbidity, livedo reticularis, thrombocytopenia, persistently positive antiphospholipid antibodies, and lesions consistent with ischemia favor antiphospholipid syndrome. Isolated low-titer antibodies are not sufficient for diagnosis.
Primary angitis of the central nervous system ¹¹	Subacute headache, cognitive or behavioral change, seizures, encephalopathy, and recurrent multifocal neurologic deficits or strokes, usually without evidence of systemic vasculitis.	MRI is usually abnormal and may show multifocal infarctions of different ages, hemorrhage, leptomeningeal enhancement, or mass-like lesions. CSF commonly shows mild pleocytosis or elevated protein. Angiography may demonstrate multifocal arterial narrowing and dilatation but lacks specificity; brain or leptomeningeal biopsy provides the greatest diagnostic specificity.	Recurrent ischemic lesions in multiple vascular territories, hemorrhage, inflammatory CSF, and angiographic or histopathologic evidence of vasculitis favor primary CNS angitis. Infection, reversible cerebral vasoconstriction syndrome, malignancy, and systemic vasculitis must be excluded.
CADASIL ¹²	Migraine with aura, recurrent lacunar strokes at a young age, mood disturbance, progressive cognitive impairment, and an autosomal-dominant family history.	MRI typically shows symmetric confluent white-matter hyperintensities, characteristically involving the anterior temporal poles and external capsules, with lacunes and cerebral microbleeds. Diagnosis is established by identifying a pathogenic NOTCH3 variant; skin biopsy may be used in selected cases.	A vascular clinical course, family history, temporal-pole and external-capsule involvement, lacunes, microbleeds, and absence of inflammatory CSF favor CADASIL over MS.
Acute or subacute infectious myelitis ¹³	Myelopathy associated with fever, meningism, rash, systemic infection, immunosuppression, epidemiologic exposure, or a recent infectious illness. Viral, bacterial, fungal, and parasitic agents may cause direct or para-infectious spinal cord injury.	MRI findings are variable and may include longitudinal lesions, cord swelling, gray-matter or anterior-horn predominance, meningeal enhancement, abscesses, or associated nerve-root involvement. CSF commonly shows pleocytosis and elevated protein and may demonstrate reduced glucose. Diagnosis relies on targeted PCR, culture, serology, antigen testing, or intrathecal antibody production.	Systemic infectious features, marked CSF inflammation, hypoglycorrhachia, meningeal or radicular enhancement, immunosuppression, and pathogen detection favor infection and should delay immunosuppression until adequately investigated.

HTLV-1-associated myelopathy/tropical spastic paraparesis ¹⁴	Slowly progressive spastic paraparesis with early bladder dysfunction, gait impairment, back pain, and relatively mild sensory loss; acute relapses are not typical.	Spinal MRI may be normal or show thoracic cord atrophy and nonspecific T2 abnormalities. CSF may show mild lymphocytic pleocytosis and elevated protein. Diagnosis requires HTLV-1 infection, supported by antibodies in serum and CSF, intrathecal antibody production, or proviral-load assessment.	Chronic nonrelapsing progression, epidemiologic exposure or residence in an endemic area, early sphincter dysfunction, cord atrophy, and confirmed HTLV-1 infection distinguish HAM/TSP from inflammatory attacks of MS, NMOSD, or MOGAD.
Spinal cord infarction ¹⁵	Abrupt onset of severe spinal cord dysfunction, frequently reaching maximal deficit within 12 hours and sometimes accompanied by acute back or neck pain.	MRI may initially be normal but subsequently show diffusion restriction, longitudinal "pencil-like" T2 hyperintensity, axial anterior-horn "owl's-eye" lesions, or adjacent vertebral-body infarction. CSF is usually noninflammatory.	Hyperacute onset, severe pain, rapid nadir, diffusion restriction, vertebral-body infarction, and noninflammatory CSF strongly favor spinal cord ischemia rather than inflammatory myelitis.
Spinal dural arteriovenous fistula ¹⁶	Progressive or stepwise thoracic myelopathy, typically in middle-aged or older men, with gait dysfunction, sensory symptoms, and sphincter impairment; symptoms may worsen with exercise or increased venous pressure.	MRI commonly shows longitudinal central spinal cord edema, often extending to the conus, with cord swelling and serpiginous perimedullary flow voids or vascular enhancement. CSF protein may be substantially elevated and mild pleocytosis can occur. Spinal catheter angiography confirms the diagnosis.	Progressive rather than relapsing disease, conus involvement, prominent perimedullary vessels, and venous-congestive edema favor a dural fistula. Failure to recognize it may lead to deterioration after corticosteroid treatment and irreversible disability.
Degenerative cervical myelopathy ¹⁷	Chronic progressive hand clumsiness, loss of dexterity, gait imbalance, limb weakness or numbness, hyperreflexia, pathological reflexes, and possible neck or radicular pain.	Cervical MRI demonstrates degenerative canal narrowing with mechanical spinal cord compression, sometimes accompanied by focal T2 hyperintensity at the compressed level. Diagnosis requires concordance between clinical myelopathy and imaging evidence of cervical cord compression.	Slowly progressive symptoms, lower-motor-neuron signs at the compressed level, upper-motor-neuron signs below it, and focal mechanical compression distinguish degenerative myelopathy from inflammatory spinal cord lesions.
Vitamin B12- or copper-deficiency myelopathy ¹⁸	Subacute sensory ataxia, paresthesia, loss of vibration and proprioception, spastic paraparesis, and associated peripheral neuropathy. Risk factors include gastric surgery, malabsorption, inadequate nutrition, and excessive zinc exposure for copper deficiency.	MRI may show symmetric T2 hyperintensity of the posterior, and sometimes lateral, cervical or thoracic columns. Evaluation includes vitamin B12, methylmalonic acid and homocysteine, or serum copper, ceruloplasmin and zinc. Anemia or neutropenia supports copper deficiency but may be absent.	Symmetric tract-selective involvement, a myeloneuropathy rather than an isolated CNS syndrome, nutritional or surgical risk factors, and abnormal metabolic testing favor a deficiency state.
Paraneoplastic myelopathy ¹⁹	Subacute or insidiously progressive myelopathy, sometimes preceding recognition of the underlying malignancy and occasionally accompanied by other paraneoplastic neurologic manifestations.	MRI may show longitudinally extensive, symmetric, tract-specific T2 abnormalities with corresponding enhancement. CSF may be inflammatory. Neural antibodies, particularly CRMP5 or amphiphysin antibodies, and systematic cancer screening may identify the cause.	Continuous progression, symmetric tract-specific lesions, constitutional or oncologic findings, a compatible neural antibody, and identification of malignancy favor paraneoplastic disease over idiopathic inflammatory demyelination.
Primary CNS lymphoma and sentinel demyelinating lesions ²⁰	Focal deficits, cognitive or behavioral change, seizures, ocular involvement, or encephalopathy, especially in older or immunocompromised patients. Rarely, inflammatory-appearing "sentinel" lesions precede overt lymphoma and transiently improve with corticosteroids.	Typical MRI findings include deep or periventricular lesions with intense enhancement and diffusion restriction, although sentinel lesions may initially resemble tumefactive or multifocal demyelination. CSF cytology or flow cytometry may assist, but tissue biopsy is frequently required.	Progressive lesion evolution, restricted diffusion, homogeneous enhancement, ocular or leptomeningeal involvement, and only temporary steroid response should raise concern for lymphoma. Corticosteroids before biopsy may obscure the histopathologic diagnosis.

Adult-onset leukodystrophies and genetic leukoencephalopathies ²¹	Slowly progressive cognitive, psychiatric, pyramidal, cerebellar, autonomic, or movement disorder, frequently with a family history or systemic manifestations. Relapsing focal attacks are unusual.	MRI generally demonstrates bilateral, symmetric, confluent white-matter abnormalities with disease-specific patterns involving the corpus callosum, corticospinal tracts, deep gray structures, or specific lobar regions. Diagnosis requires exclusion of acquired causes followed by targeted metabolic, enzymatic, and molecular testing.	Chronic progression, symmetric confluent abnormalities, positive family history, systemic metabolic clues, and absence of inflammatory CSF or typical dissemination in time favor a genetic leukoencephalopathy.
Leber hereditary optic neuropathy ²²	Painless, subacute central visual loss, usually beginning in one eye and involving the fellow eye within weeks or months, predominantly in young men; maternal family history may be present.	Funduscopy may show peripapillary telangiectatic microangiopathy, vascular tortuosity, and retinal nerve-fiber-layer swelling. Optical coherence tomography demonstrates early macular ganglion-cell loss. Diagnosis is confirmed by mitochondrial DNA testing, particularly for one of the three primary LHON variants.	Painless sequential bilateral central visual loss, dyschromatopsia, characteristic retinal findings, maternal inheritance, and a pathogenic mitochondrial variant favor LHON over inflammatory optic neuritis.

Caption: ADEM, acute disseminated encephalomyelitis; AQP4-IgG, aquaporin-4 immunoglobulin G; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CNS, central nervous system; CRMP5, collapsin response mediator protein 5; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; HTLV-1, human T-lymphotropic virus type 1; LHON, Leber hereditary optic neuropathy; MOGAD, MOG antibody-associated disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; PCR, polymerase chain reaction.

TABLE S2 - Overview of acute and long-term treatment of MS, AQP4-IgG-positive NMOSD, and MOGAD

Condition	Treatment of acute attacks	Long-term treatment	Main therapeutic implications of accurate diagnosis
Multiple sclerosis ²³⁻²⁵	Clinically significant relapses are generally treated with high-dose methylprednisolone. Plasma exchange may be considered for severe attacks with an insufficient response to corticosteroids.	Disease-modifying therapy should be initiated and individualized according to the clinical phenotype, inflammatory activity, prognostic factors, safety profile, comorbidities, reproductive plans, and patient preferences. Treatment response should be monitored, with escalation or switching when disease activity persists.	Early confirmation of MS allows timely initiation of disease-modifying therapy and reduction of further inflammatory activity. However, MS therapies should not be initiated solely on the basis of nonspecific symptoms or MRI lesions without adequate exclusion of alternative diagnoses.
Neuromyelitis optica spectrum disorder ^{26,27}	Acute attacks require prompt treatment with high-dose intravenous methylprednisolone. Plasma exchange should be started early in severe attacks or when recovery after corticosteroids is incomplete and may be considered from the outset in particularly disabling presentations.	Because disability predominantly results from attacks, long-term relapse-prevention therapy is generally recommended after the first attack in AQP4-IgG-positive disease. Options include approved targeted therapies against complement, CD19-positive B cells, or the interleukin-6 receptor, as well as rituximab and conventional immunosuppressants such as azathioprine or mycophenolate mofetil.	NMOSD attacks are frequently severe and may leave irreversible visual or motor disability. Prompt recognition enables early rescue therapy and relapse prevention, whereas misclassification as MS may expose patients to an inadequate long-term strategy.
MOG antibody-associated disease ²⁸⁻³⁰	Acute attacks are usually treated with high-dose intravenous methylprednisolone. Plasma exchange or intravenous immunoglobulin may be used in severe attacks or when the response to corticosteroids is incomplete.	Maintenance treatment is individualized because the disease may be monophasic or relapsing. Long-term immunotherapy is mainly considered after recurrent attacks, incomplete recovery, or a particularly severe presentation. Commonly used strategies include intravenous immunoglobulin, rituximab, mycophenolate mofetil, and azathioprine, although comparative evidence remains limited.	Correct distinction from MS and NMOSD prevents unnecessary or inappropriate chronic treatment. Because relapse risk varies substantially, maintenance therapy should balance the previous attack burden, residual disability, subsequent disease course, and treatment-related risks.

Caption: This table provides a simplified therapeutic overview and is not intended to replace individualized specialist assessment. Treatment selection should consider attack severity, recovery, disease course, comorbidities, safety, local availability, and patient preferences. AQP4-IgG, aquaporin-4 immunoglobulin G; MOGAD, MOG antibody-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.