CNS inflammatory demyelinating disorders: MS, NMOSD and MOG antibody associated disease

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ABSTRACT

Although Multiple Sclerosis is the most common central nervous system (CNS) inflammatory demyelinating disorder, other CNS inflammatory disorders should be included as diagnostic considerations. Neuromyelitis Optica Spectrum Disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease are less common but share some clinical characteristics, such as optic neuritis and myelitis, which can make a specific diagnosis challenging. However, these disorders have distinctive and generally different clinical phenotypes, prognosis and management. It is imperative to distinguish each from one another, especially since the treatments (not discussed in this review) can be different. The advent of reliable testing for anti-aquaporin-4 for NMOSD and anti-MOG antibodies has helped significantly; however, diagnosis can remain challenging, especially in sero-negative cases. Clinical indicators are important to guide diagnostic work-up. Careful review of the history, neurological exam, imaging, and/or spinal fluid results are essential to making an accurate diagnosis. In this review, we will examine the clinical presentation, diagnosis, and natural history of these inflammatory CNS disorders.

INTRODUCTION

Multiple sclerosis (MS) is the most common central nervous system (CNS) inflammatory demyelinating disorder. Clinically and pathologically distinct from MS, Neuromyelitis Optica Spectrum Disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG) antibody (Ab)-associated disease are also included among inflammatory CNS demyelinating disorders, though are much less common. MS, along with other demyelinating diseases including acute disseminated encephalomyelitis, transverse myelitis and optic neuritis (ON), has long been recognized within this category of important neurological diseases. However, recently the importance of other demyelinating diseases such as NMOSD and MOG associated disease has been appreciated. This review will focus on recent, key developments in MS, NMOSD and MOG-Ab associated disease diagnosis. Therefore, treatment for these disorders is beyond the scope of this article and one is referred to recent reviews on those subjects.[1–3]

With the advent of specific antibody testing, we are now better able to distinguish between MS, NMOSD, and MOG-Ab associated disease; however, diagnostic uncertainty is common due to overlapping symptomatology, particularly in sero-negative NMOSD individuals. In this review, we will examine the clinical presentation, diagnosis, and natural history of these inflammatory CNS demyelinating disorders, all of which are often characterized by a relapsing course in adults.

MULTIPLE SCLEROSIS

Background and epidemiology

MS is a chronic, immune-mediated neurodegenerative disease characterized by inflammation-induced damage primarily to myelinated nerves in the brain (including optic nerves) and spinal cord resulting in axonal loss and neurodegeneration. This process affects different areas of the CNS (ie, dissemination in space (DIS)) over time (ie, dissemination in time (DIT)) and the diagnosis of MS is still based on these primary premises.[4] Damage to myelin can affect both the gray and white matter.[5] No exact trigger for MS has been identified, though several risk factors have been recognized, to include Epstein-Barr virus, low vitamin D, early-life obesity, and cigarette smoking.[6] Although MS is not transmitted through classic Mendelian inheritance, greater than 200 genetic variants have been associated with MS, most frequently at the HLA-DRB1*15:01 locus.[7] The normal prevalence is approximately 1 in 300 persons in the USA.[8] The presence of an immediate family member with MS, increases the chance of developing MS by roughly 10 fold. MS more commonly affects young adults and while the age range has classically been referred to as 15 to 50, MS is often identified in younger children and older adults. Women are affected three times more frequently than men.[9] It has been estimated that over 2 million people worldwide have MS and around 500,000 in the USA[10]; however, based on observed increases in prevalence over time, there is recent strong evidence that rates have been underestimated with the US prevalence actually closer to 900,000.[8] It is noteworthy that in general there are geographical differences suggesting that distance from the equator relates a higher prevalence.[8] These differences may be related to amounts of sun exposure.

Table 1 Diagnostic criteria for multiple sclerosis

Clinical presentation	Additional data needed for MS diagnosis
Relapse/attack at onset	
≥2 clinical attacks and ≥2 lesions with objective clinical evidence	None
≥2 clinical attacks and one lesion plus historical evidence of attack in different location	None
≥2 clinical attacks and evidence of 1 lesion with objective clinical evidence	Dissemination in space—demonstrated by an additional clinical attack implicating a different CNS site **or** by MRI*
One clinical attack and ≥2 lesions with objective clinical evidence	Dissemination in time—demonstrated by an additional clinical attack **or** by MRI†**or** demonstration of CSF-specific oligoclonal bands‡
One clinical attack and one lesion with objective clinical evidence	Dissemination in space—demonstrated by an additional clinical attack implicating a different CNS site **or** MRI* AND Dissemination in time—demonstrated by an additional clinical attack **or** MRI†**or** demonstration of CSF-specific oligoclonal bands‡
Progression at onset	
Progression from onset (primary progressive MS)	1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse. PLUS two of the following: ► One or more T2-hyperintense lesions characteristic of MS in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial. ► Two or more T2-hyperintense lesions in the spinal cord. ► Presence of CSF-specific oligoclonal bands.

Adapted from Thompson *et al*[12].
*MRI evidence of DIS—≥1 T2 hyperintense lesions characteristic of MS in ≥2 of four areas of the CNS: periventricular, cortical or juxtacortical, infratentorial brain, and spinal cord.
†MRI evidence of DIT—simultaneous presence of enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium enhancing lesion on a follow-up MRI with reference to a prior/baseline MRI.
‡CSF-specific oligoclonal bands can substitute for the requirement of DIT.
CNS, central nervous system; CSF, spinal fluid; DIS, dissemination in space; DIT, dissemination in time; MS, multiple sclerosis.

Regardless, MS is the leading cause of non-traumatic disability among young adults and so is of special note to all health professionals who will inevitably encounter a patient with this diagnosis. The accurate and timely diagnosis of MS and related demyelinating diseases is particularly important because there are effective treatments for these diseases.

Clinical presentation—signs/symptoms

Commonly, the presenting symptoms, or clinical attack (aka, relapse or exacerbation), can include ON, brainstem syndromes (eg, double vision or other cranial neuropathy), cerebellar syndrome (eg, ataxia), or spinal cord syndromes with limb weakness and/or sensory loss[11]; however, demyelinating lesions can occur anywhere in the CNS resulting in neurological signs and symptoms. Symptoms are typically subacute and last for at least 24 hours; however, the presentation can also be slowly progressive with no recovery. Strictly speaking, certainty in diagnosing an MS attack dictates that symptoms be accompanied by objective findings either on neurological examination or imaging (ie, enhancing MS lesion on MRI) in the absence of fever or infection.[12]

Optic neuritis

The optic nerve is the most commonly involved cranial nerve in MS. ON typically presents as a unilateral loss of visual acuity (+/-central scotoma), commonly accompanied by pain with eye movements that progresses over days and then resolves over days to weeks.[13] ON can also occur bilaterally; however, this is less common and should prompt consideration for alternate etiologies such as NMOSD, Leber's hereditary optic neuropathy, or MOG Ab-associated disease, among others.[11] On examination an afferent pupillary defect with decreased color vision and diminished visual acuity will often be seen. Depending on the location of the inflammation along the optic nerve tract, there may also be evidence of inflammation of the optic disc on fundoscopic examination.[14]

Brainstem and/or cerebellar syndrome

A demyelinating lesion in the brainstem can cause cranial nerve (CN) signs/symptoms due to involvement of the cranial nerve nucleus and/or fasciculus prior to leaving the brainstem. Eye movement abnormalities are common in multiple sclerosis. Intranuclear ophthalmoplegia (INO) can be found with a careful extraocular muscle examination. An INO is helpful in gaining diagnostic certainty because it is a classic MS sign, although not exclusive to MS. The lesion is typically located in the midbrain affecting the medial longitudinal fasciculus. This results in diplopia due to difficulty adducting the ipsilateral eye and horizontal nystagmus of the abducting contralateral eye.[15 16] In MS, INOs are commonly bilateral, resulting in a presentation characterized by a wall-eyed bilateral INO syndrome. This is practically pathognomonic for MS. An isolated CN6 palsy resulting in diplopia can occur as well.[15] Additional eye movement abnormalities resulting in nystagmus or other saccadic intrusions can originate from cerebellar lesions. Trigeminal neuralgia (TN) or facial sensory loss can occur; however, isolated TN is uncommon.[17] Vertigo can present due to CN8/vestibular pathway involvement. Cerebellar lesions can result in limb and/or gait ataxia.[17 18] Dysarthria and/or dysphagia in MS can occur due to brainstem involvement of the lower CNs while ataxic and/or scanning speech can occur due to cerebellar involvement.

Spinal cord syndrome

In multiples sclerosis, demyelinating lesions of the spinal cord are typically characterized by asymmetric symptoms owing to lesions that are often partial and peripherally displaced.[17] Motor and sensory deficits can occur and would be expected to localize at or below the level of involvement in the spinal cord. Involvement of a sensory level should always prompt examination for a spinal cord

lesion. Occasionally patients will describe an electric shock sensation through the body due to a high cervical lesion, referred to as Lhermitte's sign,[19] or a sense of tightness across the chest localizing to the level of the spinal cord lesion, referred to as a 'MS hug'. Autonomic disturbances can be seen and bowel/bladder involvement is frequently associated.[20]

Other common MS-related signs/symptoms

- Weakness/Spasticity. In MS, weakness is in an upper motor neuron pattern and can occur in the setting of brainstem or spinal cord involvement; however, cerebral brain syndromes can also lead to weakness. In general, MS related weakness is usually accompanied by increased deep tendon reflexes and spasticity apparent on examination. Spasticity is common, presenting in over half of MS patients and resulting in symptoms of pain, spasm, stiffness and gait disorders.[21]
- Bowel/bladder/sexual dysfunction. Bowel and/or bladder dysfunction has been reported in 80% of MS patients. The most common urinary problems are urinary tract infections (UTIs), frequency, urgency, urge incontinence and difficulty emptying the bladder.[22] Constipation and fecal incontinence are the most common bowel complaints.[23] Sexual dysfunction is under-diagnosed in MS patients (estimates of 50%–80% in women and 65%–90% in men) and most commonly involves decrease in sexual desire and impaired arousal among women, and erectile dysfunction among men.[24]
- Cognition. Although non-specific, cognitive impairment affects up to 70% of MS patients, most commonly in the areas of information processing, processing speed, executive functioning and attention.[25] Usually cognitive dysfunction is mild and, in any case, should prompt investigation of other treatable causes.
- Fatigue. Fatigue affects up to 80% of MS patients and is one of the most commonly reported MS-related symptoms.[26 27] Patients are typically most affected in the early afternoon and worsened by heat. Symptoms can persist despite adequate sleep and are unrelated to activity; however, fatigue is also often complicated by comorbidities such as pain, depression and medication effects.
- Tremor. It is estimated that tremor affects nearly half of MS patients and can be severely disabling due to its effects on coordination.[28] Postural and intention tremors of the upper extremity are most common.[29]
- Additional symptoms encountered in MS include tonic spasms, heat intolerance, pseudo-bulbar affect, sleep-related difficulties (eg, insomnia, restless legs and obstructive sleep apnea), and higher rates of depression.

Diagnosis

When evaluating patients with possible MS, it is important to obtain a complete neurologic history and exam in order to assess for current and prior neurologic signs/symptoms which can establish disease activity over time. Finding evidence of two lesions in space on exam can be difficult, but if there is evidence of ON (eg, afferent pupillary defect) and any other central neurological sign (eg, asymmetric deep tendon reflexes) then the examiner has essentially demonstrated two lesions in space, provided there is no other explanation (eg, neurosarcoidosis) for these findings.

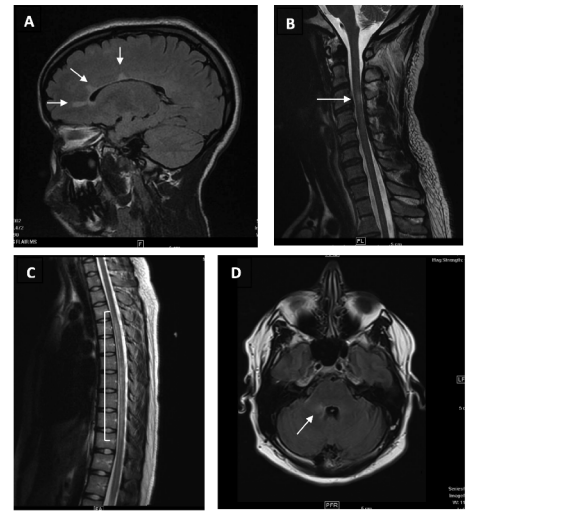

Figure 1 MRI Characteristics of MS, NMOSD, and MOG-Ab associated disease. (A) Sagittal T2 FLAIR MRI brain demonstrating periventricular lesions extending perpendicularly (ie Dawson's fingers) in a MS patient; (B) Sagittal T2 MRI C-spine with short-segment peripheral dorsal cord lesion at C3 in a MS patient; (C) Sagittal T2 MRI T-spine demonstrating LETM T3–T10 in NMOSD patient; (D) Axial T2 FLAIR MRI brain demonstrating poorly demarcated 'fluffy' lesion in the right cerebellar peduncle of a patient with MOG-Ab associated disease. FLAIR, fluid-attenuated inversion recovery; LETM, longitudinally-extensive transverse myelitis; MS, multiple sclerosis; MOG-Ab, myelin oligodendrocyte glycoprotein-antibody; NMOSD, Neuromyelitis Optica Spectrum Disorder.

Neuroimaging

Diagnostic criteria rely heavily on MRI findings in order to make an earlier and more accurate diagnosis. In fact, when applying current diagnostic criteria, it is possible to diagnose MS from a single scan, although it is important to emphasize that the diagnosis can only be certain in the presence of neurological symptoms that correlate with signs of MS on exam and/or imaging.[12] It is therefore recommended that all patients undergoing work-up have MRI completed unless there is some contraindication. Brain MRI findings suggestive of MS tend to include well-circumscribed ovoid areas of increased signal (ie, lesions) on T2 fluid-attenuated inversion recovery sequences in the periventricular regions, among other areas. Involvement of the corpus callosum and temporal horns is especially suggestive.[30 31] When the periventricular and/or callosal junction lesions extend perpendicularly into the white matter, they are often referred to as Dawson's fingers (figure 1). In addition to the periventricular region, other locations where MS demyelinating plaques are often seen, and therefore included in the diagnostic criteria, are the juxtacortical (U-fibers) brain regions, infratentorial region (especially cerebellar peduncles), and spinal cord.[12] MS lesions affecting the spinal cord are more often short-segments in the upper cervical cord, partial (involving less than half of the diameter),

Table 2 MS differential diagnosis[11 14 15 18 31 105–107]

MS presentation	Clinical course	MRI findings
Optic neuritis ► Neurosarcoidosis, SLE, CRION, Behcet's disease, NMOSD, MOG-associated disease, ADEM, neuroretinitis, infectious*, compressive pathology, vascular†, Toxic-metabolic†† , Genetic- LHON Brainstem syndrome ► Malignancy, neurosarcoidosis, NMOSD, Behcet's disease, histiocytosis, CLIPPERS, SLE, infectious‡, vascular, CPM Spinal cord syndrome ► Compression, NMOSD, neurosarcoidosis, SLE, Sjogrens Syndrome, infectious§, vascular¶	Relapsing-remitting ► Neurosarcoidosis, NMOSD, Behcet's disease, SLE, Antiphospholipid Syndrome, Sjogren's Syndrome, Lyme Disease, Vasculitis, CADASIL, LHON Progressive ► B_{12} deficiency, Copper deficiency, Paraneoplastic Syndromes, HTLV, Whipple Disease, SCA, Friedrich Ataxia, ALS or PLS, Celiac Sprue, Leukodystrophies, HSP, dural AV fistula	Small vessel disease Migraine CADASIL Susac Syndrome ADEM NMOSD Vasculitis and Inflammatory ► Primary CNS, vasculitis, SLE, Sjogren's Syndrome, Neurosarcoidosis, Neuro-Behcet's, CLIPPERS, Wegener's, Crohn's disease, Celiac disease Infectious** CPM PRES Wernicke B_{12} deficiency Mitochondrial disorders Adult-onset leukodystrophies Neoplasm

*Syphilis, Lyme, HIV, *Bartonella henselae*, neurocysticercosis, TB.
†AION, PION, GCA diabetic retinopathy, Susac syndrome, vascular malformations.
‡Infections—syphilis, listeria, Lyme, Whipple's, TB, viral.
§Syphilis, Lyme, TB, HIV, HTLV.
¶Ischemia, AVM.
**PML, HIV, Lyme, Whipple's, neurosyphilis, cysticercosis, toxoplasmosis.
††B_{12} deficiency, methanol, ethambutol, ethylene glycol.
ADEM, acute disseminated encephalomyelitis; AION, anterior ischemic optic neuropathy; ALS, amyotrophic lateral sclerosis; AV, arteriovenous; AVM, arteriovenous malformation; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CPM, central pontine myelinolysis; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CRION, chronic relapsing inflammatory optic neuropathy; GBS, Guillain-Barre syndrome; GCA, giant cell arteritis; HTLV, human T-lymphotropic virus; LHON, Leber's hereditary optic neuropathy; NMOSD, neuromyelitis optica spectrum disorder; NO, nitrous oxide; PION, posterior ischemic optic neuropathy; PLS, primary lateral sclerosis; PRES, posterior reversible encephalopathy syndrome; SCA, spinocerebellar ataxia; SLE, systemic lupus erythematosus; TB, tuberculosis.

and peripherally located with the dorsolateral cord often involved (figure 1).[18 31] The presence of a longitudinally extensive lesion and/or complete/central involvement, while possibly MS, should prompt consideration for an alternate etiology.[11] MRI mimickers of MS are common, and one of the most commonly encountered mimickers are white matter lesions in the brain due to chronic microvascular ischemic disease. These lesions are more often small (ie, less than 3 mm), punctate and non-ovoid, symmetric, located in the subcortical or deep gray matter (corpus callosum usually spared), and would not be expected to involve the spinal cord or result in contrast-enhancement.[31] Rarely, demyelinating lesions affecting the brain can be large with swelling and mass effect and an overall appearance similar to that seen with a brain tumor, termed 'tumefactive MS.' In these cases, biopsy is occasionally required for diagnosis.[32] Contrast (ie, gadolinium) is usually administered to assess for acute/active lesions which remain 'enhancing' for up to 8 weeks with a majority resolving within 4 weeks.[33] Lesions that continue to enhance beyond 8 weeks should raise suspicion for an alternate diagnosis such as sarcoidosis or malignancy.

Spinal fluid (CSF) analysis

In addition to excluding an underlying infectious and/or alternate inflammatory disorder, CSF analysis can help to provide supportive evidence that there is an underlying inflammatory condition specific to the CNS. CSF appearance and opening pressure are typically normal. A mild lymphocyte-predominant pleocytosis can be seen.[34] Oligoclonal bands that are present in the CSF but absent in the serum suggest an immune response that is restricted to the CNS. Up to 95% of those with clinically definite MS have CSF-specific oligoclonal bands and this predicts a higher rate of progression to MS in those with a clinically-isolated syndrome.[35–37]

Additional work-up considered on a case-by-case basis

For example, one may need to evaluate for systemic autoimmune conditions that can result in CNS demyelinating lesions such as systemic lupus erythematosus (SLE) or Sjogren's disease. Lyme disease, tuberculosis, HIV, and/or human T-lymphotropic virus testing may be considered based on the history obtained. In the setting of a strong family history, leukodystrophies may be included in the differential (eg, arylsulfatase A, long-chain fatty acids, hexosaminidase A and/or B). Testing for NMO IgG and/or anti-MOG-Ab may be obtained if there is a NMOSD-type phenotype (see the Neuromyelitis Optica Spectrum Disorder section). Ophthalmologic exam may be considered for a detailed exam, to include optical coherence tomography, which can reveal abnormalities supportive of MS (eg, retinal nerve fiber layer thinning).[38] Chest imaging should be obtained if there is concern for neurosarcoidosis.

Once conditions other than MS have been excluded or deemed unlikely, then it is appropriate to apply the McDonald's criteria for MS diagnosis. The goal is to establish evidence of inflammatory neurologic episodes separated

Box 1 NMOSD diagnostic criteria.

NMOSD with AQp4-IgG
1. At least one core clinical characteristic.
2. Positive AQP4-IgG.
3. Exclusion of alternative diagnosis.

NMOSD without AQP4-IgG or unknown status
1. At least two core clinical characteristics from one or more clinical attacks and fulfilling the following requirements: (a) At least one of either ON, LETM or APS (b) Dissemination in space (c) MRI requirements if applicable.
2. Negative AQP4-IgG.
3. Exclusion of alternative diagnosis.

Core criteria
1. ON.
2. Acute myelitis.
3. APS.
4. Acute brain stem syndrome.
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions.
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions.

Supporting MRI Requirements for NMOSD without AQP4-IgG or with unknown status
1. Acute ON: (a) normal brain MRI or non-specific white matter lesions, OR (b) optic nerve T2-hyperintensities or T1-weighted gadolinium-enhancing lesion 1/2 optic nerve length or involving chiasm.
2. Acute myelitis: MRI lesion extending over ≥3 contiguous segments, or spinal cord atrophy ≥3 contiguous segments with history compatible with acute myelitis.
3. APS with associated MRI lesions in medulla/area postrema.
4. Brain stem syndrome with associated peri-ependymal brainstem lesion.

Adapted from Wingerchuck et al[68].
APS, area postrema syndrome; AQP4-IgG, antibody to aquaporin-4 antibody; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; LETM; longitudinally extensive transverse myelitis.

by time (DIT) and space (DIS; affecting different areas of the CNS). While the history and exam can establish DIS and DIT (eg, patient with prior history of ON who now presents with spinal cord syndrome), MRI can be especially useful for this purpose. MRI evidence of DIS can be established by having at least one lesion in at least two of the following areas: periventricular, cortical or juxtacortical, infratentorial, or spinal cord.[12] MRI evidence of DIT can be established in one of two ways, either by the presence of an enhancing and non-enhancing lesion, or by the development of a new lesion seen on a follow-up MRI compared with a prior/baseline scan.[12] When making an initial diagnosis, the provider must determine whether there has been a relapsing-remitting (RRMS) onset versus a primary progressive (PPMS) onset as these each have separate diagnostic criteria (table 1). Both RRMS and PPMS are discussed in additional detail in the next section.

A detailed overview of the differential diagnosis of MS is beyond the scope of this paper; however, when evaluating a patient for potential MS and considering alternatives, it is often useful to consider the MS presentation (eg, ON), the clinical course (eg, relapsing-remitting vs progressive), and the MRI findings. A brief overview of what to consider in the differential diagnosis based on the aforementioned factors can be seen in table 2

Clinical course and classifications

As previously mentioned, the first clinical attack in multiple sclerosis is referred to as a clinically isolated syndrome (CIS). The differential diagnosis for CIS may include monophasic demyelinating diseases such as idiopathic ON, idiopathic transverse myelitis, or acute disseminated encephalomyelitis (ADEM). The risk of developing a second attack resulting in a diagnosis of clinically-definite MS varies and is heavily influenced by the presence of typical MS lesions seen on MRI at the time of evaluation; up to 80% of those with typical demyelinating brain MRI abnormalities will develop definite MS.[17]

Clinically-definite MS is further categorized into at least three subtypes to include RRMS, secondary-progressive (SPMS), and PPMS. RRMS is the most common type of MS diagnosed at onset (approximately 85%) and is characterized by recurrent episodes of neurologic impairment followed by recovery (can be complete or incomplete) in between episodes. Incomplete recovery occurs approximately 40% of the time resulting in residual impairment that can lead to disability over time.[39] Relapses are typically accompanied by corroborating MRI findings to include new or enlarging contrast-enhancing lesions. It is noteworthy that, in untreated patients, for every new symptomatic lesion seen on MRI, there may be several times more asymptomatic 'clinically-silent' lesions that accumulate.[40] MS relapses, whereby there is a new neurologic symptom attributable to an area of active inflammation affecting the brain, optic nerves or spinal cord, tend to occur with higher frequency earlier in the disease course, diminishing in frequency as the disease progresses. Pseudo-relapses are temporary episodes of neurologic impairment that are not due to underlying CNS inflammation and usually characterized by the re-emergence and/or worsening of previously experienced MS-associated signs/symptoms. This most commonly occurs in the setting of infection (eg, UTI) and/or elevated body temperature and appears to be due to conduction block in abnormal axons.[41]

SPMS occurs after the patient has initially exhibited a RRMS course. These patients exhibit a progressive disability over time, with or without relapses, and typically develop gait impairment. The estimated time to SPMS ranges from 10 to 20 years, with older age at diagnosis being associated with shorter time to onset.[42] There has been suggestion that the prognosis of MS is improving with the increasing use of disease-modifying treatment.[43] It was previously believed that a large majority of those that start out with RRMS would eventually develop SPMS (up to 80% after 20 years); however, a more recent estimate suggests rates much lower (15%–30%).[44 45]

PPMS, in contradistinction to SPMS, is characterized by disease progression from the very onset and a large majority

Table 3 Comparison between MS, NMOSD, and MOG-Ab associated disease

	MS	NMOSD	MOG-Ab
Approx. age at onset[99–101]	30s	40s	30s
Female: male[9 69 93]	3:1	9:1	1.3:1
Coexisting autoimmune disease[94]	Rare	Common	Rare
Clinical Course[100]	Relapsing or progressive	Relapsing	Monophasic or relapsing
ON[69 94 99 102]	Usually mild with good recovery Bilateral simultaneous ON is rare Long-segment involvement is rare	Usually severe with limited recovery Bilateral simultaneous ON is common Can be longitudinally extensive	Usually severe with good recovery Bilateral simultaneous ON is very common Can be longitudinally extensive
Transverse myelitis[94 99 102 103]	Short-segment and partial/peripherally located	Usually LETM and centrally located	LETM or short-segment; central involvement is common Conus involvement can be characteristic
Brain lesions[100 102 104]	Lesions adjacent to the body of the lateral ventricle (especially inferior temporal lobe) Ovoid lesion with perpendicular alignment to the lateral ventricle (ie, Dawson's fingers) Subcortical U-fiber lesions	Variable: ► can appear normal and/or non-specific ► hypothalamic, periaqueductal grey and area postrema lesions seen	Variable: ► can appear normal and/or non-specific ► can appear similar to ADEM ► 'fluffy', that is, poorly demarcated T2-hyperintensities
CSF-specific OCBs[37 69 88 92 93 100]	Common (up to 95%)	Less common (up to 30%)	Uncommon (up to 12%)

ADEM, acute disseminated encephalomyelitis; LETM, longitudinally-extensive transverse myelitis; MS, multiple sclerosis; NMO, neuromyelitis optica; OCBs, oligoclonal bands; ON, optic neuritis.

of these individuals present with a gait disorder.[46] PPMS occurs in approximately 15% of all MS patients and can occur with or without relapses (ie, PPMS with active disease vs PPMS without active disease).[12 46] All-in-all, PPMS tends to occur at a later age and infers a worse prognosis relative to RRMS.[47 48]

Radiologically isolated syndrome (RIS) describes a situation where there are MRI lesions suggestive of MS; however, there are no associated clinical episodes or symptoms.[49] It is estimated that 34% of those with RIS will go on to develop symptoms and a diagnosis of MS within 5 years.[50]

NEUROMYELITIS OPTICA SPECTRUM DISORDER

Background and epidemiology

Neuromyelitis optica (NMO) was first described by Devic in the late 19th century as a disorder of simultaneous ON with myelitis.[51] NMO was thought to be a variant of multiple sclerosis, however the discovery of a biomarker, antibody to aquaporin-4 (AQP4-IgG), in 2004 provided a reliable way to distinguish between the two diseases.[52 53] The diagnosis of NMO originally required the simultaneous presence of myelitis and ON. This later evolved to NMOSD, a group of inflammatory conditions including classic NMO as well as broader phenotypes. At presentation, shared features of MS and NMOSD such as transverse myelitis and ON can be difficult to distinguish clinically. However, there are characteristic clinical signs and diagnostic findings that help distinguish between these disorders. Additionally, the diagnosis, clinical course and treatment of these two disorders are distinctly different. The incidence and prevalence of NMOSD is significantly lower than multiple sclerosis with the yearly incidence 0.053–0.40 per 100,000 and prevalence 0.52–4.4 per 100,000[54–59] based on pre-2015 criteria. Using the broader 2015 criteria, yearly incidence was 0.037–0.39 and prevalence 0.89–4.1 with increased rates in some countries when compared with 2006 criteria.[60–65] There is a stronger female predominance in NMO/NMOSD and higher non-Caucasian predominance than is seen in MS.[66 67]

Clinical presentation—signs/symptoms

While NMO was classically defined by simultaneous ON and transverse myelitis, NMOSD incorporates other phenotypes. Core clinical characteristics include ON, acute myelitis, area postrema and/or other brainstem syndrome, diencephalic, and cerebral signs/symptoms.[68] ON and transverse myelitis are the most common symptoms at disease onset, with no significant difference between AQP4-IgG seropositive and seronegative patients.[69] In addition to intractable nausea and vomiting, brainstem involvement can also cause hearing loss, diplopia, olfactory dysfunction, vertigo, facial palsies or other cranial nerve dysfunction.[69 70] Sleep abnormalities and narcolepsy can occur due to involvement of deep gray structures like the hypothalamus.[71 72]

Optic neuritis

When compared with ON with MS (ON-MS), ON with NMOSD (ON-NMOSD) has been found to have distinctive patterns. Patients commonly presented with isolated ON as their initial symptom[73–75] but ON-NMOSD has also been associated with a higher rate of bilateral ON that can occur simultaneously or sequentially.[52 69 76] ON-NMOSD is also associated with poorer tong-term outcome compared with ON-MS.[77] On MRI, ON-NMOSD involves longer segments of the optic nerve and can involve the optic chiasm.[67 78] AQP4-IgG seropositivity is associated with more severe visual impairment at both presentation and follow-up. Seropositivity is also associated with increased recurrence of ON and likelihood of developing subsequent transverse myelitis.[76]

Transverse myelitis

Longitudinally-extensive transverse myelitis (LETM) was formerly a diagnostic requirement for NMO and remains one of the core clinical characteristics for diagnosis.[68]Compared with multiple sclerosis, myelitis in NMOSD is characteristically more extensive in length, and more commonly affects the central cord and gray matter rather than the peripheral areas (figure 1).[79 80] LETM is a term applied to myelitis involving at least three contiguous vertebral segments. Although more common in MS, shorter segment transverse myelitis can also occur in NMOSD.[66 81] In a large study of imaging findings in NMOSD and MS, there was a similar percentage of patients with at least one spinal cord lesion (72.2%, 67.7%).[81] In both MS and NMOSD, location of spinal cord lesions was more common in the cervical cord than the thoracic cord. The majority of patients with NMOSD have only partial or no recovery from myelitis, with only 17% achieving a complete recovery regardless of AQP4-IgG status.[69]

Area postrema syndrome (APS)

The area postrema, located in the dorsal medulla, is responsible for the emetic reflex as well as other autonomic regulatory functions.[82] Inflammation in this area can cause persistently episodic nausea, vomiting and hiccups referred to as APS when lasting>48 hours. APS is seen as the initial symptom in 7.1%–10.3% of AQP4-IgG-seropositive NMOSD patients.[83] Additionally, it is seen in up to 30% of patients at some point during their disease course. Symptoms can fluctuate over months and can require hospitalization for intravenous antiemetics and rehydration.

Diagnosis

Diagnostic criteria for NMO (aka Devic's syndrome), proposed in 1999, required simultaneous ON and acute myelitis in the absence of other findings in the CNS.[73] After AQP4-IgG was identified as a specific biomarker in NMO, the classic phenotype was subsequently broadened.[52 53] Diagnostic criteria were revised in 2006 to remove restriction from CNS involvement outside of optic nerves and spinal cord as well as incorporating AQP4-IgG seropositivity in supportive criteria.[84]

In 2007, NMOSD was coined to describe AQP4-IgG positive patients who did not meet criteria for NMO or had atypical presentations of NMO. NMOSD also includes AQP4-IgG positive patients with coexisting autoimmune disorders such as systemic lupus erythematous and Sjogren's syndrome.[85] Diagnostic criteria were further revised in 2015 and included unifying NMO and NMOSD into consensus criteria for NMOSD with AQP4-IgG and NMOSD without AQP4-IgG.[68]

The revision of diagnostic criteria in 2015 further expanded those that are classified as NMOSD to include a larger assortment of clinical manifestations. Additionally, patients are classified as either NMOSD with AQP4-IgG, NMOSD without AQP4-IgG, or unknown. Diagnostic criteria within these subtypes are summarized in box 1.

Serum antibody testing should be ordered on patients who have features of NMOSD without suspicion of an alternative diagnosis. A meta-analysis showed cell-based assay testing of AQP4-IgG is superior to tissue-based assays or ELISA testing with approximated sensitivity of 0.76 and mean specificity 0.99.[86] A lumbar puncture is often performed in initial diagnostic stages when evaluating for inflammatory conditions such as MS or NMOSD. However, serum testing has been shown to be more sensitive for the presence of AQP4-IgG.[87] In a large study of AQP4-IgG positive patients, only 16.4% of patients were found to have CSF-restricted oligoclonal bands. Total protein CSF levels were increased in 52.6% of cases and approximately half of patients had a CSF pleocytosis that was typically mild.[88]

Clinical course and classification

As discussed previously, patients with NMOSD can be further classified by the presence or absence of AQP-4 antibodies. Most patients with NMOSD have a relapsing course, while a secondary progressive course is uncommon.[69 73 89] However, clinical course can vary with the presence or absence of AQP4- IgG. Seropositive patients with ON or TM at disease onset have a significantly higher rate of relapsing course (92.7%) as compared with seronegative patients (76.3%). More than half of patients presenting with first-event LETM who are AQP4-IgG positive will go on to have a recurrence or develop ON within the next 12 months.[53] Overall, mean time from first symptom until relapse is 8.5 months without significant difference between seropositive and seronegative groups.[69]

MYELIN OLIGODENDROCYTE GLYCOPROTEIN-ANTIBODY ASSOCIATED DISEASE

Background and epidemiology

MOG is expressed on the external surfaces of myelin and oligodendrocytes in the CNS. Some patients with clinical features of NMOSD who are negative for AQP4-IgG may be found to have antibodies against MOG (MOG-IgG). Thus, MOG-Ab testing should be considered in patients with an NMOSD phenotype with negative AQP4-IgG. In one study, approximately 40% of those testing negative for AQP4-IgG were positive for MOG-IgG.[90] The median age of onset ranges from 6 to 36 years with MOG-Ab associated disease.[91–93]Compared with NMO AQP4-IgG positive patients, there is a lower female predominance (44% female).[94]

Clinical presentation—signs/symptoms

Isolated ON is the most common symptom at onset (55%–61%) of which almost half are bilateral.[92 93] Transverse myelitis is typically longitudinally extensive like NMOSD, but more often affects the thoracic spinal cord and conus medullaris rather than cervical spinal cord as is seen in MS and AQP-IgG positive NMOSD.[94 95] ADEM can be seen in MOG-Ab associated disease, with higher prevalence in younger patients. In one large cohort, 18% of patients with MOG-Ab presented with ADEM as their initial symptom. Furthermore, ADEM was the most prevalent symptom at presentation in patients younger than 20 at disease onset.[93]

Diagnosis

Serum cell-based assays have been shown to have the highest sensitivity for MOG-Ab. CSF testing is not recommended as CSF MOG-IgG is found in only 67% of seropositive patients, suggesting that the anti-MOG antibodies have

a peripheral origin.[96] Antibody titers can vary depending on disease activity with higher levels during attacks; although MOG-Ab can persist even with monophasic disease.[92 96] Other CSF findings with MOG-Ab are similar to CSF findings with AQP4-IgG positive NMOSD.[95]

Brain lesions seen with MOG-Ab associated disease are poorly demarcated or 'fluffy', and more likely to be found in the brainstem or cerebellar peduncles than those with MS (figure 1).[97] However, MOG-Ab brain lesions are not easy to distinguish from those seen in AQP4-IgG positive NMOSD patients. MS, NMOSD and MOG-Ab associated disease have overlapping differential diagnosis with certain clinical presentations as shown in table 2.

Clinical course

In MOG-Ab associated disease, the clinical course is relapsing in approximately 34%–80% of cases.[91–93 95 98]Compared with AQP4-Ab positive NMOSD there are fewer patients with long-term visual and motor disabilities.[94] However, nearly half of patients are left with some form of permanent disability, including decreased visual acuity, impaired mobility, or bladder and bowel dysfunction.[93] A summary of more commonly encountered differentiating features between MS, NMO, and MOG-Ab associated disease has been outlined in table 3.

CONCLUSION

MS is the most common CNS demyelinating disorder; however, NMOSD and MOG-Ab associated disease remain diagnostic considerations in a subset of patients. Highly suggestive characteristics of NMOSD and MOG-Ab associated disease include LETM, bilateral and/or severe ON, or poor recovery, among other clinical presentations discussed above. When there are positive antibodies (eg, anti-NMO, anti-MOG), the diagnosis is straightforward as there is little evidence to support the co-occurrence of these three conditions. In particular, double positivity for AQP4-IgG and MOG antibodies was not seen in large comparative studies.[95 96] On the other hand, it can be more difficult to distinguish between MS and seronegative NMOSD. This is where a careful review of the history, exam, imaging, and/or CSF results are essential to making an accurate diagnosis. In addition, referral to a MS specialist should always be considered since the diagnosis and treatment of these conditions is challenging.

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