MS VARIANTS AND MIMICS

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Multiple sclerosis (MS) is a chronic disease with neuroinflammatory and neurodegenerative characteristics. There is no single diagnostic test for MS. A clinician must insure that a patient has an appropriate clinical history and examination findings and diagnostic test results compatible with MS. Accurate diagnosis is crucial to avoid providing a patient with an incorrect prognosis and inappropriate therapy. There are numerous diagnoses that can mimic MS symptoms, signs, MRI findings, and CSF results; case examples will be shown. This syllabus provides a brief summary of key differential diagnostic considerations, which can be summarized by addressing 2 key questions:

1. Is it a rare MS presentation or a non-MS CNS idiopathic inflammatory demyelinating disease?

A. ADEM and Atypical MS Presentations

Acute disseminated encephalomyelitis (ADEM) and tumefactive (tumor-like) MS presentations can considerations in individuals with acute, severe, and often first clinical presentations of CNS inflammatory disease.[1,2] ADEM is almost always a monophasic disorder that presents with multifocal CNS disease, encephalopathy with depressed level of consciousness, and may follow a viral illness or vaccination. Brain MRI shows white matter lesions affecting both white and gray matter and most or all lesions will enhance after gadolinium administration. Tumefactive MS describes a clinical syndrome dominated by a subacute, progressive focal neurological syndrome (e.g., hemiparesis), associated with a focal, tumor-like brain MRI lesion. In some instances, the clinical history suggests prior events consistent with MS or the brain MRI reveals currently asymptomatic lesions that are highly characteristic for MS. However, at times such clinical and MRI features are absent and concern about a primary glioma or other mass lesion prompts brain biopsy that ultimately reveals inflammatory demyelination.

B. Neuromyelitis Optica Spectrum Disorder (NMOSD)

Neuromyelitis optica spectrum disorder (NMOSD) is an idiopathic CNS inflammatory demyelinating disease the hallmarks of which are optic neuritis and transverse myelitis.(3) NMOSD has been definitively established as distinct from MS, primarily based on the evidence that NMO is associated with antibodies directed against the astrocyte water channel aquaporin-4 (these antibodies are known as NMO-IgG or AQP4-IgG) but MS is not. Serum AQP4-IgG testing is about 75% sensitive and more than 90% specific for NMO. Moreover, several lines of evidence show that AQP4-IgG is likely pathogenic and the immunopathology of NMO differs from that of MS.(4,5)

Despite these differences, NMO and MS have some overlapping clinical and neuroimaging characteristics. NMO-related optic neuritis tends to be more severe than in MS and to affect posterior optic nerves and/or the optic chiasm as compared to the anterior optic nerve pattern usually seen with MS. Transverse myelitis in NMOSD is usually “longitudinally extensive” (LETM) with concurrent detection of a spinal cord MRI lesion that extends over 3 or more vertebral segments and affects the central cord. In contrast, MS-associated myelitis is usually associated with a short-segment MRI lesion (1 vertebral segment or less) and peripherally located in the cord, preferentially affecting the dorsal columns. There are exceptions; in one series, up to 15% of first-ever events of myelitis in patients with NMOSD did not meet the 3-segment criterion, although MRI lesions in subsequent attacks did.(6)

The advent of the AQP4-IgG biomarker has facilitated observations regarding an expanded clinical phenotype of NMO, which has been termed “NMO spectrum disorders” (NMOSD).(3) It also has allowed observation that brain MRI may show signature patterns with involvement of the dorsal medulla/area postrema (associated with intractable hiccups, nausea, and vomiting) and lesions of the diencephalon and cerebrum.

Revised Diagnostic Criteria for NMOSD

The International Panel for Neuromyelitis Optica Diagnosis (IPND) proposed revised consensus diagnostic criteria in 2015 [7]. There was a perceived need to update the 2006 criteria because of advances in understanding the full clinical and neuroimaging spectrum of the disease, informed by associations with AQP4-IgG, and to allow for earlier confirmation of the diagnosis to facilitate earlier preventive treatment. The new criteria are meant for clinical use and to guide future research endeavors, especially to better understand the heterogeneous AQP4-IgG seronegative group.

The new criteria use a single term, NMOSD, stratified by AQP4-IgG status. Therefore, patients are diagnosed with NMOSD with AQP4-IgG or NMOSD without AQP4-IgG. Because there are world regions where access to AQP4-IgG testing is limited or nonexistent, the IPND concluded that defining a seronegative group was important because it had treatment implications, specifically, that patients not be misdiagnosed with MS and potentially treated with one of the MS disease-modifying therapies that may aggravate NMOSD. The term "NMOSD with unknown AQP4-IgG status" can be used for patients who meet the NMOSD without AQP4-IgG criteria but who have not been tested for AQP4-IgG. In addition, the criteria allow for NMOSD with AQP4-IgG diagnosis after a single clinical attack has taken place; this allows for earlier diagnostic confirmation and treatment compared with the 2006 criteria.

The diagnosis of NMOSD with AQP4-IgG requires a positive serological test together with a clinical syndrome indicating involvement of at least one of 6 neuroanatomically-based CNS regions: optic nerve, spinal cord, area postrema of the dorsal medulla, brain stem, diencephalon, and cerebrum (Table 1). The 3 most common presentations (spinal cord, optic nerve, and area postrema) do not require MRI confirmation of any specific lesion pattern. Importantly, a transverse myelitis event associated with a non-LETM lesion (i.e., less than 3 contiguous vertebral segments in length) can qualify a AQP4-IgG seropositive patient for confirmed disease. A single brain stem attack can also be sufficient to meet criteria in seropositive patients. Involvement of the diencephalon or cerebrum, both of which are less common and less specific symptomatically, require additional neuroimaging support, specifically findings of "NMOSD-typical" lesions.

NMOSD without AQP4-IgG diagnosis has more stringent criteria (Table 1). Involvement of 2 of 6 neuroanatomic regions is required. Although this could occur with one attack (e.g., classic Devic's syndrome of simultaneous LETM and optic neuritis), in practice it is most likely to be accomplished through multiple attacks. Spinal cord lesions must be meet LETM criteria (unlike AQP4-IgG seropositive patients).

Particular care is required to exclude competing disorders, especially in AQP4-IgG seronegative cases. The paper that describes the new criteria emphasizes "red flags" that should alert the clinician to alternative diagnoses. In both seropositive and seronegative cases, a final requirement is that there is no better explanation for the clinical syndrome than NMOSD. Interpretation of AQP4-IgG serology results is an important component of the criteria and is discussed in the paper as well as in the Scientific Update syllabus associated with this course. Some AQP4-IgG seronegative patients have serum antibodies directed against myelin oligodendrocyte glycoprotein (MOG) and may have somewhat different characteristics (more equal sex ratio, more frequent monophasic course, more grey matter and lower cord involvement) and several groups are studying the natural history and appropriate categorization of such patients.

Table 1. NMOSD Diagnostic Criteria for Adult Patients

Diagnostic Criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses

Diagnostic Criteria for NMOSD without AQP4-IgG or NMOSD with Unknown AQP4-IgG Status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
    a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
    b. Dissemination in space (2 or more different core clinical characteristics)
    c. Fulfillment of additional MRI requirements, as applicable
2. Negative test(s) for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses

Core Clinical Characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
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

Additional MRI Requirements for NMOSD without AQP4-IgG and NMOSD with Unknown AQP4-IgG Status

1. Acute optic neuritis: requires brain MRI showing a) normal findings or only nonspecific white matter lesions; or b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending over $\geq$3 contiguous segments (LETM) or $\geq$3 contiguous segments of focal spinal cord atrophy in patients with prior history compatible with acute myelitis
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. Acute brain stem syndrome: requires associated peri-ependymal brain stem lesions

Recently, a group of AQP4-IgG seronegative patients with a clinical NMOSD phenotype has been shown to have serum antibodies to myelin oligodendrocyte glycoprotein (MOG). (8,9) Validation studies are ongoing.

2. Is it a specific other disease mimicking MS?

The increased dependence on MRI in the assessment of possible MS cases allows for an earlier diagnosis, but can add to diagnostic uncertainty. In addition, the potential costs and risks of disease modifying therapies make it important to be aware of common MS mimics and to recognize clinical red flags and imaging characteristics that are associated with alternative diagnoses. (10-12) Table 2 lists several MRI abnormalities that warrant a consideration of an alternative diagnosis.

TABLE 2: MRI findings suggestive of a non-MS diagnosis

MRI "Red Flag"	Alternative Diagnoses
White matter	
Hemorrhages/microhemorrhages	Amyloid angiopathy; Moya Moya disease; CADASIL; vasculitis
Selective anterior and temporal lobe involvement	CADASIL
Persistent Gd enhancement	Lymphoma; glioma; vasculitis; sarcoidosis
Simultaneous enhancement of all lesions	Vasculitis; lymphoma; sarcoidosis; ADEM
Lacunar infarcts	Hypertensive ischemic disease; CADASIL; Susac syndrome
Complete ring enhancement	Brain abscess; glioblastoma; metastatic cancer
Diffuse white matter involvement	Behcet's disease; HIV; small vessel disease; CADASIL
Large lesions starting in juxtacortical location with progressive enlargement	PML
Lesions in the temporal pole, U-fibers, external capsule, insula	CADASIL
Extensive and bilateral periventricular abnormalities in isolation	B12 deficiency; acquired copper deficiency
Gray Matter	
Cortical Infarcts	Embolic disease; Thrombotic thrombocytopenic purpura (TTP); vasculitis
T2-hyperintensity in the Dentate Nucleus	Cerebrotendinous xanthomatosis
T1-hyperintensity of the pulvinar	Fabry disease; hepatic encephalopathy; manganese toxicity
Large, infiltrating brainstem lesions	Behcet's disease; pontine glioma
Predominance of lesions at cortical/subcortical junction	Embolic infarction; vasculitis; progressive multifocal leukoencephalopathy (PML)
Multiple discrete lesions of the basal ganglia and thalamus	Susac's syndrome
Spinal Cord	
Large lesions with mass effect	NMO; ADEM; acute transverse myelitis; Sjogren's syndrome
Diffuse abnormalities in the posterior columns	Vitamin B12 deficiency; acquired copper deficiency
Other	
Cerebral Venous Sinus Thrombosis	Behcet's disease; vasculitis; chronic meningitis; hypercoagulable state
Meningeal enhancement	Chronic meningitis; Sarcoidosis; lymphomatosis; Primary angiitis of the CNS; Lyme disease
Calcifications on CT scans	Neurocysticercosis; toxoplasmosis; mitochondrial disorders
Hydrocephalus	Sarcoidosis
Dilation of Virchow-Robin spaces	Hyperhomocysteinemia; Primary angiitis of the CNS
Regional atrophy of the brainstem	Behcet's disease; adult onset Alexander's disease

Adapted from references 10 and 11.

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