The Diagnosis and Classification of Multiple Sclerosis

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Disclosures

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The Diagnosis and Classification of Multiple Sclerosis

- Epidemiology & Pathophysiology
- Terminology & MS Subtypes
- 2017 McDonald Criteria
- MS Mimics & the Differential Diagnosis (Briefly)
Multiple Sclerosis

**Definition and Epidemiology**
- Acquired disorder of the central nervous system characterized by the destruction of myelin and neurodegeneration and resultant loss of neurological function
- Prevalence: 309/100,000 in the USA
- Prevalence: 70/100,000 Internationally
- North - South predilection

Wallin et al Neurology 2019
MS - Pathogenesis

- Autoimmunity/Inflammation
- Neurodegeneration
- Genetics
- Environmental
Multiple Sclerosis - Diagnosis

There must be no better explanation!!! (MS mimic red flags)
MS Diagnosis – Laboratory – Oligoclonal bands (OCBs)

- ≥2 oligoclonal IgG bands detected by separation of cerebrospinal fluid (CSF) proteins while not demonstrable in corresponding serum
- A local B-cell response accompanying central nervous system inflammation.
- Use protein separation by isoelectric focusing followed by immunoblotting,
- ≥ 95% of patients with MS have CSF OCBs of IgG class not detectable in serum

**Oligoclonal Bands in CSF**

<table>
<thead>
<tr>
<th></th>
<th>CSF</th>
<th>Plasma</th>
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<tbody>
<tr>
<td>Oligoclonal</td>
<td></td>
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<tr>
<td>Bands present</td>
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<tr>
<td>Oligoclonal</td>
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<tr>
<td>Bands absent</td>
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John Rose, M.D., Maria Houtchens
The Diagnosis and Classification of Multiple Sclerosis

- Epidemiology & Pathophysiology
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Multiple Sclerosis - Diagnosis

There must be no better explanation!!! (MS mimic red flags)
Terminology – Diagnosis of MS

- **Clinically Isolated Syndrome (CIS)** is a first episode of neurologic symptoms typical of an MS relapse in a person not known to have MS.
CIS to MS

- Long term risk (45% to 75%)
- Gold standard for diagnosis was 2nd event
- 3 large prospective CIS natural hx studies
  - 1. ONTT (n=388)
    - @ 10 yrs - 38%
  - 2. UK study (mixed CIS) (n=109)
    - @ 10 yrs - 59%
  - 3. Spain study (mixed CIS) (n=156)
    - @ 7 yrs - 42%

Beck et al NEJM 1992
Optic Neuritis Study Group 2006
Fisniku et al Brain 2008
Tintore et al Neurology 2006
CIS to MS

KEY IS MRI LESIONS

1. ONTT (n=388)
   - +MRI = 56% @ 10 yrs vs 22% w/ -MRI
2. UK study (mixed CIS) (n=109)
   - +MRI = 82% @ 20 yrs vs 21% w/ -MRI
3. Spain study (mixed CIS) (n=156)
   - +MRI = 60% @ 7 yrs vs 8% w/ -MRI
Multiple Sclerosis - Diagnosis

There must be no better explanation!!! (MS mimic red flags)
Diagnosis – MS – Radiological Hyperintense lesion on T2-weighted MRI

Images courtesy of Daniel Pelletier, MD
What are typical MS MRI lesions?

- >3 mm²
- Ovoid, well circumscribed, homogeneous signal, asymmetric
- Periventricular regions
  - Radial orientation away from the ventricles
  - Involves paracentral corpus callosum, but NOT midline
- Juxtacortical
- Infratentorial
  - Floor of 4th ventricle, surface of the pons
- Spinal Cord
  - Peripheral
  - Dorsolateral cord
  - <2 vertebral segments
  - <½ of cross-sectional cord area
- Enhancement typically lasts 4-6 weeks
What characteristics point us away from MS?

- Nonspecific white matter changes
  - Punctate
  - Nonovoid
  - Frequently located in subcortical regions
- No spinal cord lesions
Why do we want to diagnose MS patients as early as possible?

- **BENEFIT 11 study (Betaseron)**
  - Risk of conversion from CIS→CDMS reduced by 33% in early treatment group
  - Kaplan-Meier estimate of risk of SPMS at 11 years of follow-up (25 pts)
    - 4.5% in early treatment group
    - 8.3% in delayed treatment group

- **MSBase Study**
  - Conversion from RRMS to SPMS up to 17 year follow up
    - 29% early treatment group
    - 47% later treatment group

Kappos L et al Neurology 2006
Brown et al JAMA Neurology 2019
MS Subtypes and Natural History

CIS: Radiologically Isolated Syndrome

RIS: Radiologically Isolated Syndrome

Clinical Threshold

NMSS advisory committee-1996

Lublin et al Neurology 2013
1996 MS clinical description Subtypes

Relapsing-remitting disease (RRMS)

With sequelae/residual deficit after incomplete recovery

With full recovery from relapses

2013 MS disease modifiers Phenotypes

Clinically isolated syndrome (CIS)

Not active*

Active*, **

Relapsing-remitting disease (RRMS)

Not active*

Active*
<table>
<thead>
<tr>
<th>1996 MS clinical description Subtypes</th>
<th>2013 MS disease modifiers Phenotypes</th>
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<tbody>
<tr>
<td>Progressive accumulation of disability from onset with or without temporary plateaus, minor remissions and improvements</td>
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</tr>
<tr>
<td>Progressive accumulation of disability after initial relapsing course, with or without occasional relapses and minor remissions</td>
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<tr>
<td>Progressive accumulation of disability from onset but clear acute clinical attacks with or without full recovery</td>
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</tr>
<tr>
<td>PP</td>
<td>Progressive accumulation of disability</td>
</tr>
<tr>
<td>SP</td>
<td>Active* and with progression**</td>
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<tr>
<td>(PP)</td>
<td>Active but without progression</td>
</tr>
<tr>
<td>(SP)</td>
<td>Not active but with progression</td>
</tr>
<tr>
<td></td>
<td>Not active and without progression (stable disease)</td>
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</table>
Myelocortical: A new subtype of MS

- Cortical neuronal loss (neurodegeneration) independent of cerebral white matter demyelination
- Loss of myelin in the cerebral cortex and spinal cord

Trapp BD et al Lancet 2018
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2017 Revisions to the McDonald Criteria

- Increased sensitivity (how many patients with MS are identified as having MS), decreased specificity (how many healthy people are identified as NOT having MS)

Cohen & Thompson Lancet 2017
Multiple Sclerosis - Diagnosis

Clinical

Laboratory (CSF)

Radiological

There must be no better explanation!!! (MS mimic red flags)
Multiple Sclerosis - Diagnosis - Clinical

- Typical Syndromes – MS-related demyelinating attack/relapse
  - Optic neuritis
  - Brainstem syndromes (e.g. Trigeminal neuralgia)
  - Cerebellar syndromes
  - Transverse myelitis
Multiple Sclerosis - Diagnosis - Clinical

- Objective clinical evidence
  - CNS lesion corresponding to the presentation of an attack
- Examples:
  - Afferent pupillary defect for vision loss → optic neuritis
  - Internuclear ophthalmoplegia for diplopia → brainstem syndrome
  - Hemisensory level in patient with sensory/motor symptoms → transverse myelitis
Isolated brainstem syndrome

Typical for MS
Internuclear ophthalmoplegia, sixth nerve palsy, multifocal signs (e.g., facial sensory loss and vertigo or hearing loss)

Atypical for MS
Hyperacute onset, vascular territory signs (e.g., lateral medullary syndrome, age >50, isolated trigeminal neuralgia, fluctuating ocular/bulbar weakness, nonremitting, fever, meningism)

Brain MRI

Normal
Low risk for MS

Abnormal
Lesions consistent with demyelination
High risk for MS
Review McDonald criteria

MRI clearly indicates a non-MS diagnosis (e.g., hemorrhage)

Consider other diagnoses

Ischemic/hemorrhagic (e.g., cavernous malformation)
Infiltrative
Inflammatory (e.g., sarcoid, lupus)
Infection (e.g., syphilis, listeria, Lyme, virus)
Toxic
Nutritional
Central pontine myelinolysis
Neuromuscular (e.g., myasthenia gravis)

MRI, CSF, neurophysiologic, serologic, and other studies as appropriate

Adapted from: Solomon Continuum 2019
Adapted from: Solomon Continuum 2019

Isolated spinal cord syndrome

Typical for MS
- Evolution over hours to days
- Partial myelitis
- Purely sensory
- Deafferented upper limb
- Lhermitte sign
- Partial Brown-Séquard syndrome
- Spontaneous remission

Atypical for MS
- Hyperacute onset or insidiously progressive
- Complete transverse myelitis
- Sharp sensory level
- Radicular pain
- Areflexia
- Failure to remit

MRI clearly indicates a non-MS diagnosis (e.g., spinal cord compression)

Brain and spinal cord MRI

Normal
- Low risk for MS

Abnormal Lesions consistent with demyelination
- High risk for MS
  - Review McDonald criteria

Consider other diagnoses

- Compression (e.g., intervertebral disk, tumor)
- Ischemia/infarction
- Other inflammatory (e.g., neuromyelitis optica, sarcoid, lupus, Sjögren syndrome)
- Infection (e.g., syphilis, Lyme, virus, tuberculosis)
- Toxic/nutritional/metabolic (e.g., vitamin B12 deficiency, nitrous oxide toxicity, copper deficiency)
- Arteriovenous malformation
- Noncord “mimics” (e.g., Guillain-Barré syndrome, myasthenia gravis)

MRI, CSF, neurophysiologic, serologic, and other studies as appropriate
Primary Progressive MS - Clinical

- 10-15% of patients will have a progressive course from the onset of symptoms
- A small proportion will have infrequent attacks
- At least 1 year of disability progression independent of any disability from a relapse
Concepts: 2017 McDonald Criteria

- **Dissemination in time (DM):**
  - Can be demonstrated in a single MRI scan with simultaneous gadolinium-enhancing and nonenhancing lesion OR
  - Appearance of a new T2-hyperintense or gadolinium-enhancing lesion on a follow-up MRI scan (irrespective of timing of either scan) OR
  - Demonstration of 2 or more oligoclonal bands in the cerebrospinal fluid (CSF)

- **Dissemination in space (DIS):**
  - Detection of the presence of T2-hyperintense MRI lesions in four areas of the CNS, including (1) periventricular, (2) cortical or juxtacortical, and (3) infratentorial brain regions and (4) the spinal cord.
  - The presence of at least one T2-hyperintense MRI lesion in **two of these regions demonstrates dissemination in space**. This can include the symptomatic lesion
    - Eg. if a patient has a clinical myelitis and a corresponding spinal cord lesion on MRI, we only need 1 more T2-hyperintense lesion in either the periventricular, cortical/juxtacortical or infratentorial brain region
  - The anterior vision system is NOT included in 2017 criteria for demonstration of MRI dissemination in space
What Are the Key Changes from 2010?

In individuals with typical CIS:

- **CSF oligoclonal bands** -- Positive findings of oligoclonal bands in the spinal fluid can substitute for demonstration of dissemination of lesions in time in some settings.

- **Types of lesions** – Both asymptomatic and now symptomatic MRI lesions can be considered in determining dissemination in space or time. *(This does not include MRI lesions in the optic nerve in a person presenting with optic neuritis.)*

- **Site of lesions** – Cortical lesions have been added to juxta cortical lesions for use in determining MRI criteria for dissemination of lesions in space.
In a person with a typical attack/CIS event

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Criteria to Make MS Diagnosis</th>
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<tbody>
<tr>
<td>• 2 or more attacks and clinical evidence of 2 or more lesion; OR</td>
<td>None, DIS and DIIT have been met</td>
</tr>
<tr>
<td>• 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location</td>
<td></td>
</tr>
<tr>
<td>• 2 or more attacks and clinical evidence of 1 lesion</td>
<td>DIS shown by one of these criteria:</td>
</tr>
<tr>
<td></td>
<td>• Additional clinical attack implicating different CNS site</td>
</tr>
<tr>
<td></td>
<td>• 1 or more MS-typical T2 lesions in 2 or more areas of the CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord</td>
</tr>
<tr>
<td>CLINICAL PRESENTATION</td>
<td>ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------------------</td>
</tr>
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</table>
| • 1 attack and clinical evidence of 2 or more lesions | DIT shown by one of these criteria:  
• Additional clinical attack  
• Simultaneous presence of both enhancing and nonenhancing typical MRI lesions, or new T2 or enhancing MRI lesions compared to baseline scan (without regard to timing of baseline scan)  
• CSF oligoclonal bands |
| • 1 attack and clinical evidence of 1 lesion | DIS shown by one of these criteria:  
• Additional attack implicating different CNS site  
• 1 or more MS-typical T2 lesions in 2 or more areas: periventricular, cortical, juxtacortical, infratentorial or spinal cord  
**AND**  
DIT shown by one of these criteria:  
• Additional clinical attack  
• Simultaneous presence of both enhancing and nonenhancing typical MRI lesions, or new T2 or enhancing MRI lesions compared to baseline scan (without regard to timing of baseline scan)  
• CSF oligoclonal bands |
In a person with steady progression of disease since onset:
  Primary Progressive MS

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<th>ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS</th>
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<tr>
<td>1 year of disease progression (retrospective or prospective)</td>
<td>DIS shown by at least two of these criteria: - 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) - 2 or more T2 spinal cord lesions - CSF oligoclonal bands</td>
</tr>
</tbody>
</table>
The Panel Also Recommended That:

• Brain MRI should be obtained during the MS diagnostic process, unless not possible. Spinal MRI should be obtained when additional data are needed to confirm the diagnosis.

• When spinal fluid is used as part of the diagnostic process, paired serum and CSF samples be analyzed to confirm that oligoclonal bands are unique to the CSF.

• At the time of diagnosis, the MS course should be indicated, and whether the course is active or not, and progressive or not; and the type and course of MS should be reevaluated periodically as the disease evolves.
Caveats to the diagnosis of MS

- MS is best diagnosed by a clinician with MS-related expertise with support of imaging and other tests.
- Ensure there is no better explanation
- The McDonald Diagnostic Criteria apply to individuals experiencing a typical clinically isolated syndrome – CIS
- The accuracy of oligoclonal band testing in the cerebrospinal fluid depends on methodology employed
  - A lab that performs agarose gel electrophoresis with isoelectrical focusing and immunoblotting or immunofixation for IgG is recommended
- Use caution when considering historical symptoms in the absence of supportive objective evidence of a CNS lesion

National MS Society (nationalmssociety.org)
Case #1

- A 21 year old Caucasian woman presents with a 3 day history of right vision loss. She awoke 3 days ago with blurry vision in the right eye, which gradually worsened throughout the day. She also has periocular pain worsened by eye movements.

- On exam she has a right afferent pupillary defect and visual acuity is 20/100 in the right eye. The remainder of her exam is normal.

- MRI shows enhancement of the right optic nerve and four ovoid T2 hyperintense lesions (1 juxtacortical, 3 subcortical). There is a small posterior C4 T2 hyperintense lesion that does not enhance.

- CSF analysis shows 9 oligoclonal bands restricted to the CSF.
In a person with a typical attack/CIS event

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  • Simultaneous presence of both enhancing and nonenhancing typical MRI lesions, or new T2 or enhancing MRI lesions compared to baseline scan (without regard to timing of baseline scan)  
  • CSF oligoclonal bands |
| • 1 attack and clinical evidence of 1 lesion  | DIS shown by one of these criteria:  
  • Additional attack implicating different CNS site  
  • 1 or more MS-typical T2 lesions in 2 or more areas: periventricular, cortical, juxtacortical, infratentorial or spinal cord  
  **AND**  
  DIT shown by one of these criteria:  
  • Additional clinical attack  
  • Simultaneous presence of both enhancing and nonenhancing typical MRI lesions, or new T2 or enhancing MRI lesions compared to baseline scan (without regard to timing of baseline scan) |
Next step? Does this patient have MS?

- No red flags for other diagnosis than MS
- Optic neuritis: typical syndrome for clinical attack in MS
  - Dissemination in space (need T2 hyperintense lesion in 2/4 regions):
    - Brain MRI fulfills one (juxtacortical lesion) out of four regions for MRI dissemination in space
    - Spine MRI fulfills one (C4 lesion) out of four regions for MRI dissemination in space
  - Dissemination in time:
    - She **does not** have 2 clinical attacks OR simultaneous enhancing and nonenhancing hyperintense T2 lesions on MRI (again bc optic nerve is excluded) BUT she does have
  - Positive OCBs in the CSF
Does this patient have MS?

- This patient has fulfilled 2017 McDonald Diagnostic criteria for Multiple Sclerosis despite having only had 1 clinical attack.
The Diagnosis and Classification of Multiple Sclerosis

- Epidemiology & Pathophysiology
- Terminology & MS Subtypes
- 2017 McDonald Criteria
- **MS Mimics & the Differential Diagnosis (Briefly)**
MS Mimics - Differential Diagnosis Considerations

**Inflammatory/Autoimmune**
- Neuromyelitis optica
- MOG IgG
- Acute disseminated encephalomyelitis
- Sarcoidosis
- Systemic lupus erythematosus
- Polyarteritis nodosa
- Granulomatosis with polyangiitis
- Giant cell arteritis
- Susac’s syndrome
- Sneddon’s syndrome (APLA syndrome)
- CIDP
- Bickerstaff brainstem encephalitis
- Chronic lymphocytic inflammation with pontine perivascular enhancement (CLIPPERS)
- Cogan’s syndrome (Vasculitis)
- Behcet Disease
- Sjogren Syndrome

**Vascular**
- Migraine variants
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Moyamoya
- Binswanger’s disease
- Small vessel disease of HBP and DM
- Intravascular lymphoma
- Cerebroretinal vasculopathy
- Ischemic optic neuropathy

**Neoplastic**
- Metastatic brain disease
- Glioma and gliomatosis cerebri
- Primary CNS lymphoma
- Intravascular lymphoma
- Paraneoplastic syndromes

Singhal D, Berger J R 2012; Solomon 2018 & 2019
MS Mimics - Differential Diagnosis Considerations

**Infectious**
- Lyme disease
- Neurosyphilis
- Toxoplasmosis
- HTLV-1 myelopathy
- Progressive multifocal leukoencephalopathy (PML)
- Subacute sclerosing panencephalitis
- HIV
- Brucellosis
- Human herpes virus, type 6
- Coxsackie virus encephalitis
- Variant CJD

**Mitochondrial disorders**
- Leigh’s disease
- Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
- Mitochondrial encephalopathy with lactic acidosis (MELAS)

**Metabolic**
- Vitamin B12 deficiency
- Vitamin E deficiency
- Copper deficiency
- Porphyria
- Wilson’s disease
- Adrenoleukodystrophy and adrenomyeloneuropathy
- Metachromatic leukodystrophy
- Fabry’s disease
- Krabbe’s disease
- Leukoencephalopathy with neuroaxonal spheroids
- Adult polyglucosan disorder

Singhal D, Berger JR 2012; Solomon 2018 & 2019
MS Misdiagnosis

- Up to 20% of patients are misdiagnosed
- Exposure to unnecessary disease modifying therapy
- Psychological burden
- Delay in making the “real” diagnosis

Kaisey M et al MS and Rel Dis 2019
Solomon et al 2012 and 2016;
How to prevent a misdiagnosis of Multiple Sclerosis

**Typical Demyelinating Syndromes**

- MS diagnostic criteria should be applied only in the typical demyelinating syndromes in which they have been validated.
- Caution should be taken in patients older than 50 years of age (or younger than 11 years of age) and in nonwhite populations.
- Continue to consider a broad differential diagnosis, with vigilance for red flags, even in patients with typical syndromes.

Adapted from: Solomon et al 2018
How to prevent a misdiagnosis of Multiple Sclerosis

Rely on “The 5 Principles”:
1. “Typical” syndrome for MS
2. Objective evidence of CNS involvement
3. Dissemination in space
4. Dissemination in time
5. No better explanation
How to prevent a misdiagnosis of Multiple Sclerosis

Use of Prior Symptoms for Fulfillment of Dissemination in Time Criteria

- Objective evidence on neurologic examination or as the result of paraclinical testing (visual evoked potentials, MRI, optical coherence tomography) must corroborate symptoms

- Objective evidence specific for central nervous system demyelination, such as internuclear ophthalmoplegia or afferent pupillary defect, is preferred over nonspecific evidence such as hyperreflexia

Adapted from: Solomon et al 2018
How to prevent a misdiagnosis of Multiple Sclerosis

**MRI Lesions and Their Characteristics**
- Juxtacortical lesions must abut the cortex, without intervening white matter
- Periventricular lesions must abut the ventricles, without intervening white matter
- Lesions should be 3 mm or larger in diameter
- Small punctate lesions should not be used to fulfill MRI criteria
- Use of intracortical and subpial cortical lesions to fulfill criteria should be restricted to experienced imaging centers

Adapted from: Solomon et al 2018
How to prevent a misdiagnosis of Multiple Sclerosis

Symptomatic MRI Lesions for Fulfillment of Dissemination in Space and Dissemination in Time

- In patients with monophasic syndrome of a single symptomatic brainstem or spinal cord lesion where only one additional MRI dissemination in space region is satisfied, consider awaiting appearance of an additional MRI lesion or additional clinical event to meet dissemination in space criteria, especially when comorbidities are present.

Adapted from: Solomon et al 2018
How to prevent a misdiagnosis of Multiple Sclerosis

**CSF Evaluation**
- CSF evaluation is recommended before finalizing a diagnosis of primary progressive MS.
- Oligoclonal bands restricted to the CSF should be used with caution in the presence of high numbers of polymorphonuclear cells or highly elevated protein.
- Positive oligoclonal bands should be used to substitute for dissemination in time criteria only in patients <50 yrs presenting with optic neuritis, brainstem, or spinal cord syndromes typical for MS and without evidence of another inflammatory central nervous system condition.
- If CSF is negative for findings typical of MS, a diagnosis of MS should be made with caution.

Adapted from: Solomon et al 2018
Case 2: Is this MS?

- A 56 year old woman presents with multiple episodes of nausea and vertigo with blurry vision in both eyes lasting <24 hours. She reports a unilateral pulsating headache in association with many of these episodes. She also recalls an episode of right leg numbness radiating from the buttocks to the toes 3 years earlier that resolved after a month. Past medical history including hypertension and chronic tobacco use
Case 2 Continued

- General and neurologic examinations were normal.
- MRI demonstrates several T2-hyperintense lesions located primarily in the subcortical and deep white matter, with a few in the periventricular and juxtacortical locations as well. MRI of the Cervical and Thoracic spinal cord are normal. CSF examination is normal.
Case 2. Is this MS?

Red flags:
- Age (McDonald criteria not tested in patients >50 yrs old)
- Atypical clinical syndrome for MS
  - Brief duration of symptoms
- Normal exam
- No objective evidence of a CNS lesion that correlates with present or prior symptoms
- History of suspected migraine, HTN and tobacco use can all cause MRI abnormalities
- Normal cord imaging and CSF
- There IS DIS, but McDonald criteria cannot be applied
Case 2: Is this MS?

- She does not meet criteria for MS
- Consider white matter disease in the setting of migraine, hypertension & tobacco use
Case 3: Is this MS?

- A 25 year old African American woman presents with subacute weakness and numbness in the legs and urinary retention requiring catheterization. She progresses to needing a wheelchair 2 weeks after onset of symptoms.

- Neurologic examination reveals severe weakness in the legs and a T4 sensory level.
Case 3: Is this MS?

- CSF: WBC 28 (64% lymphocytes) (normal up to 5 cells/field); Total Protein 133 mg/dL (normal 0-35 mg/dL), negative Oligoclonal bands
- Serum aquaporin-4 (AQP4)-IgG (+)
- Diagnosis of neuromyelitis optica spectrum disorder (NMOSD) was made
- Treated with IV steroids, followed by plasma exchange, with return to ambulating independently
- Rituximab was then prescribed as maintenance medication
Clinical Features of Neuromyelitis Optica Spectrum Disorder

Cardinal Clinical Features
- Transverse myelitis, typically longitudinally extensive (≥3 vertebral segments; often followed by tonic spasms and occasionally accompanied by pain or pruritus)
- Optic neuritis (often severe; may be bilateral)
- Episodes of intractable nausea and vomiting or hiccups from area postrema involvement

Other Clinical Features
- Narcolepsy
- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- Other hypothalamic presentations (eg, anorexia)
- Acute myopathy with hyperCKemia
- Brainstem syndromes (eg, ophthalmoplegia, hearing loss [possibly related to inner ear damage] opsoclonus/myoclonus)
- Myeloradiculitis
- Encephalopathy (PRES-like; ADEM-like)
- Cognitive dysfunction (subcortical pattern [inattention, executive dysfunction, reduced speed of processing])
- Hydrocephalus

ADEM = acute disseminated encephalomyelitis; CK = creatine kinase; PRES = posterior reversible encephalopathy syndrome.
NMOSD: Clinical/Diagnostic

- Poor recovery from attacks
- Tonic spasms
- Frequent coexistence with SLE, Sjögren Syndrome, Antiphospholipid antibody syndrome, Myasthenia Gravis
- Most patients will not have typical lesions on MRI Brain, usually around 3rd and 4th ventricles (dorsal medulla/area postrema)
- About 20% of patients are AQP4 IgG (-)
- About 30% of patients have OCBs in CSF
NMOSD Diagnostic Criteria 2015

AQP4 IgG (+):
1. $\geq 1$ core clinical characteristic (Optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, narcolepsy/acute diencephalic syndrome with MRI lesions, symptomatic cerebral syndrome)

AQP4 IgG (-):
1. $\geq 2$ core clinical characteristics (at least 1 optic neuritis, LETM, area postrema syndrome)
2. Dissemination in space
3. MRI criteria (depending on clinical presentation):
   1. Normal Brain MRI or optic nerve MRI with lesion extending over more than 1/2 optic nerve length or involving chiasm
   2. MRI spinal cord lesion $\geq 3$ contiguous segments
   3. Dorsal medulla/area postrema lesions
   4. Brainstem lesions
   *Must exclude alternative diagnoses
Take Home Points

- MS is diagnosed using the 2017 McDonald Diagnostic Criteria
- These criteria have only been validated in patients WITH MS
- The importance of red flags
  - ASK QUESTIONS! GET THAT HISTORY!
  - REVIEW YOUR OWN MRIs
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- Karlo Lizarraga MD, MS
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