MULTIPLE SCLEROSIS
OVERVIEW AND DIAGNOSIS

Aliza Ben-Zacharia, PhD, DNP, ANP-BC
Assistant Professor, Co-Director Research/EBP, Mount Sinai
Assistant Professor, Hunter Bellevue School of Nursing
MS Overview and Diagnosis
Multiple Sclerosis

- Immune mediated disease of the CNS
- Affects an estimated 900,000 people in the US
- Leading cause of nontraumatic neurological disability in young adult
- Mean age of onset 20–30 years
- Female : Male ratio 3:1
- Can lead to physical disability, cognitive impairment, and decreased quality of life
- Reduces life expectancy by 7 to 14 years

Multiple Sclerosis

- Inflammation with demyelination
- Astroglial proliferation (gliosis) and neurodegeneration
- Meningeal and cortical grey matter pathology in multiple sclerosis

MS as a Silent Disease: Topographical Model

Topographical Example of Disease Progression

Lesion location

- Optic nerve, spinal cord
- Brainstem, cerebellum
- Cerebral hemispheres

Krieger SC. Poster presented at: 2015 Meeting of the CMSC; May 29, 2015; Indianapolis, IN. Poster DX47.
Normal White Matter

Images courtesy of Bruce D. Trapp.
Active Lesion

Images courtesy of Bruce D. Trapp.
Chronic Inactive Lesion

Image courtesy of Bruce D. Trapp.
Environmental and Genetic Factors

• Around 20% of the heritability risk is attributable to common genetic variants
  • HLA DRB15:01 haplotype (odds ratio (OR) of ~3)
• Smoking
• Obesity
• Low sun exposure
  • Vitamin D deficiency

Prodromal MS

Natural History of MS Pre-treatment Era

Hauser and Cree American Journal of Medicine 2020

CIS – Clinically Isolated Syndrome; EDSS - Expanded Disability Status Scale

MS Diagnosis

- MS is diagnosed on the basis of clinical findings and supporting evidence from ancillary tests.
- **Magnetic resonance imaging**: The imaging procedure of choice for confirming MS and monitoring disease progression in the CNS.
- **Evoked potentials**: Used to identify subclinical lesions; results are not specific for MS.
- **Lumbar puncture**: May be useful to support DIT; CSF is evaluated for oligoclonal bands and intrathecal immunoglobulin G (IgG) production.

DIT – dissemination in time

Difficulty in Diagnosing MS

- There is no single pathognomonic clinical feature or diagnostic test for MS
- Other conditions can mimic MS in:
  - MRI appearance
  - Clinical presentation
  - Clinical course
  - CSF findings
- Increased risk for more than 1 autoimmune condition
- Great variability in MS
  - Age of onset
  - Clinical course
  - Symptoms and signs
  - Paraclinical evidence
- Misdiagnosis of MS remains a problem in clinical practice

Typical Presenting Syndromes of MS

- **Optic Neuritis**
  - Unilateral
  - Retrobulbar pain &/or with movement
  - Recovery expected
  - No retinal exudates or disc hemorrhages

- **Myelitis**
  - Partial sensory or motor
  - Bowel and bladder dysfunction
  - Thoracic band-like sensation
  - L’hermitte’s sign

- **Brainstem/Cerebrum**
  - Ocular motor syndromes
  - Hemisensory, crossed sensory
  - Hemiparesis
  - Trigeminal neuralgia
  - Hemifacial spasms

- **Cerebellum**
  - Cerebellar tremor
  - Acute ataxia

Atypical Presenting Syndromes of MS

- Isolated 4th CN palsy
- Complete 3rd CN palsy
- Hearing loss
- Homonymous hemianopsia
- Aphasia
- Seizures
- Depressed LOC
- Progressive motor deficit
- Extrapyramidal features
- Loss of reflexes

CN – cranial nerve; LOC – locus of control
Disorders That Can Mimic MS

- **Vascular**
  - Migraine; CNS vasculitis; antiphospholipid syndrome; CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

- **Inflammatory autoimmune diseases**
  - Systemic lupus erythematosus (SLE); neuro-Behçet disease; Sjögren syndrome; sarcoidosis; Susac’s syndrome

- **Inflammatory demyelinating disorders**
  - Neuromyelitis Optica Spectrum Disorders (NMOSD’s); Anti-MOG; acute disseminated encephalomyelitis (ADEM); tumefactive MS

- **Infectious disorders**
  - Neuroborreliosis (Lyme disease); syphilis; West Nile virus; progressive multifocal leukoencephalopathy (PML); cysticercosis; HTLVI/II; HIV or herpes encephalitis

Disorders That Can Mimic MS (cont.)

- **Metabolic disorders**
  - Mitochondrial disorders (MELAS, MERRF, LHON); B12 deficiency; Wilson’s disease

- **Leukodystrophies**
  - Adrenoleukodystrophy
  - Metachromatic leukodystrophy

- **Multifocal CNS neoplasms**
  - Lymphoma; gliomastosis cerebri
  - Metastases

- **Other**
  - Spinal stenosis; central pontine myelinolysis; radiation therapy
  - Medications: adalimumab

Multiple Sclerosis Criteria

1800’s
- 1838 1st drawing

1868 Charcot

20th century
- 1969 Schumacher
- 1983 Poser

21st century
- 2001 McDonald Criteria
- 2005 McDonald Criteria
- 2010 McDonald Criteria
- 2017 McDonald Criteria

MRI as a Paraclinical tool

## 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis

<table>
<thead>
<tr>
<th>No. of Clinical attacks</th>
<th>No. of MRI lesions with objective clinical evidence</th>
<th>Additional data needed for diagnosis of multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing-remitting multiple sclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>≥2</td>
<td>None</td>
</tr>
<tr>
<td>≥2</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>≥2</td>
<td>1</td>
<td>DIS demonstrated by an additional clinical attack implicating a different CNS Site or by MRI</td>
</tr>
<tr>
<td>1</td>
<td>≥2</td>
<td>DIT demonstrated by additional clinical attack, MRI, or CSF-specific oligoclonal bands</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>DIS demonstrated by additional clinical attack implicating a different CNS site or by MRI and DIT demonstrated by an additional clinical attack or by MRI or demonstration of CSF-specific oligoclonal bands</td>
</tr>
</tbody>
</table>

**Primary progressive multiple sclerosis**

Required: 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

Plus 2 of the following: 1 or more T2-hyperintense lesions characteristic of multiple sclerosis in 1 or more of the following brain regions: periventricular cortical or juxtacortical, or infratentorial; 2 or more T2-hyperintense lesions in the spinal cord; presence of CSF-specific oligoclonal bands

---

Key changes made to the McDonald Criteria in 2017

- Brain stem and cord lesions can now be counted among the 2 lesions disseminated in space and time
- CSF oligoclonal bands can now be used to substitute for demonstration of dissemination in time in some settings
- Both asymptomatic and now symptomatic MRI lesions can be considered in determining dissemination in space (optic nerve lesions are still excluded).
- Cortical lesions have been added to juxtacortical lesions as determinant for dissemination in space

### The MS Lesion Checklist

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Present</th>
<th>Absent</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve root entry zone. The lesions that track along nerve roots, especially the trigeminal nerve root, favor an inflammatory over vascular etiology. In an active MS lesion, enhancement may extend from parenchyma into nerve proper.</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Middle cerebellar peduncle. Middle cerebellar peduncle (MCP) involvement in MS is seen frequently, but less than in the body of the pons.</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Middle cerebellar peduncle. Middle cerebellar peduncle (MCP) involvement in MS is seen frequently, but less than in the body of the pons.</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Medial longitudinal fasciculus. This tract is commonly affected in MS both clinically (inter-nuclear ophthalmoplegia [INO]) and on MRI, however, vascular etiology is more common. Bilateral internuclear ophthalmoplegia may be somewhat more common in MS compared to stroke but is seen in many conditions.</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Other brainstem lesions adjacent to cerebrospinal fluid border. &quot;With remarkable regularity the brainstem lesions [are] contiguous with the inner and outer cerebrospinal fluid (CSF) borders.&quot;</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Cerebellar hemisphere. Demyelinating cerebellar lesions are not contiguous with the CSF border, but appear within the deep cerebellar white matter. The cerebellum is often spared in vascular disease, but is commonly affected in MS, especially when the brainstem is involved.</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Inferior temporal lobe. Another area of white matter that is preferentially affected in MS compared to vascular disease.</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lesions adjacent to lateral ventricle—Dawson’s fingers. &quot;Wedge-shaped areas with broad base to the [lateral] ventricle, and extensions into adjoining tissue in the form of finger-like processes or ampullae, in each of which a central vessel could usually be found&quot;. Frontal caps and bands along ventricular surface are normal signs of aging and should not be confused with periventricular demyelinating lesions.</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Corpus callosum. Demyelination at the callosal-septal interface may take the form of discrete lesions or more diffuse lumpy-bumpy appearance (ie, dot-dash sign), which is seen on multiple sagittal FLAIR images, in contrast to the smooth appearance of the subcallosal vein that is usually only seen on a single sagittal image.</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>U-fibers (arcuate fibers). U-fiber lesions that track along arcuate fibers are particularly characteristic of demyelination and are not seen in normal aging or vascular disease.</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Other cortical/juxtacortical lesions. Plaques in cortex and at junction of cortex and white matter are very common in MS. A recent study recommended combining cortical and juxtacortical lesions for purposes of MS diagnosis. Cortical lesions may be better appreciated on double inversion recovery (DIR) sequence, which is not routinely available.</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Typical MS Lesions

Key Locations
- Periventricular
- Corpus callosum
- Cortical juxtacortical
- Cerebellar peduncle
- Cervical spine

Shape
- Oval/ovoid/\geq 3-5\text{mm}
- Dawson’s fingers

Well-demarcated
- No mass effect

Spinal cord lesions
- \textless 3 vertebral segments
- Only part of cross-section of the cord
- No extensive cord swelling

Gad enhancement
- Initially nodular
- Can evolve to a ring or an arc
  - T1 hypointense center
  - Opening of ring points toward the cortex

Demyelination and Axonal Transection on MRI

Courtesy of Bruce D. Trapp.
Oligoclonal Bands in CSF

- Presence independent predictor of CIS to RRMS and RIS to CIS or disability accumulation (HR 2.0, 95% CI 1.2–3.6) in CIS
- Patients with CIS who had 8–12 OCBs had a 2.5-fold greater risk of conversion to CD MS than patients with fewer OCBs

Revised Clinical Phenotypes

Relapsing-Remitting Disease
- Clinically Isolated Syndrome (CIS)
  - Clinically active
  - Clinically not active

- Relapsing-Remitting Disease (RRMS)
  - Relapsing-remitting active
  - Relapsing-remitting not active

Progressive Disease
- Progressive accumulation of disability from onset (PPMS)
  - Progressive active with progression
  - Progressive active no progression

- Progressive disease after initial relapsing course (SPMS)
  - Progressive not active but with progression
  - Progressive not active and no progression (stable disease)

## Relapse vs. Pseudo Relapse

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Relapse</th>
<th>Pseudo Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature</td>
<td>New or worsened symptoms, which are due to new inflammatory MS activity in the brain or spinal cord</td>
<td>Worsened neurologic symptoms; the underlying cause of the worsening is not from new immune system activity or inflammation</td>
</tr>
<tr>
<td>Timing</td>
<td>New symptoms manifest over a few hours or days and then plateau over a few days to weeks and then slowly improve over weeks to months</td>
<td>Worsened symptoms fluctuate, and especially if they resolve completely and then return</td>
</tr>
<tr>
<td>Recurrence</td>
<td>MS does not often result in repeated inflammation in the exact same part of the brain</td>
<td>The recurrence of old symptoms is more common in a pseudo relapse</td>
</tr>
<tr>
<td>Localization</td>
<td>Symptoms that can be explained by anew active MS lesion in the CNS</td>
<td>No place that a lesion in the CNS cause the symptoms/Another process: infection, medication, stress</td>
</tr>
<tr>
<td>Type of Symptoms</td>
<td>Vision loss, numbness, weakness are typical symptoms of a relapse</td>
<td>Sudden worsening of spasticity and pain are rarely due to an acute relapse</td>
</tr>
</tbody>
</table>

A common misconception is that any attack of CNS demyelination means a diagnosis of acute MS.
Confirmed MS Diagnosis

New or worsened neurologic symptoms lasting > 24 hrs

Fever, clinical and/or Lab signs of infection?

Evaluate to confirm or rule out MS relapse

If symptoms persist

No

Yes

Treat infection and re-evaluate in 7-10 days

Once MS relapse clinically confirmed – in most cases initiate systemic steroids (typically IVMP 1g for 5 days)

No response or intolerability to MP – consider repository corticotropin injection (typically 80 U IM or SQ for 5-14 days)

No response and/or severe disabling symptoms – consider plasmapheresis

Initiate DMT


IFN-la Natalizumab Fingolimod Dimethylfumarate IFN-la Daclizumab Cladribine

IFN-lb Glatiramer Acetate Teriflunomide Alemtuzumab Gen Copaxone Ocrelizumab Siponimod

IFN-la IFN-lb

Ofatumumab Ozanimod, Ponesimod

Radiological Isolated Syndrome

- Diagnosis of RIS occurs during diagnosis of another unrelated condition, such as migraine headaches or trauma to the area.
- Typical MRI MS lesions without clinical presentation.
- Two-year period, one third of patients with RIS develop a neurological event and are diagnosed with MS, one third develop a new finding on MRI without any symptoms, and one third show no change.

Clinically Isolated Syndrome

- CIS is a first episode of neurologic symptoms caused by inflammation and demyelination in the CNS.
- The episode, must last for at least 24 hours, is characteristic of multiple sclerosis but does not yet meet the criteria for a MS diagnosis because people who experience a CIS may or may not go on to develop MS.
- The 2017 McDonald criteria make it possible to diagnose MS in a person with CIS who also has specific findings on brain MRI.

Multiple sclerosis endophenotype

Presymptomatic

Symptomatic

Prediagnostic phase

At risk

Asymptomatic multiple sclerosis (RIS)

Prodromal multiple sclerosis

CIS

Multiple Sclerosis

Disease state (focal multiple sclerosis pathology)

Inflammation, demyelination, neuroaxonal loss, gliosis, and intrathecal synthesis of oligoclonal IgG

Relapsing Remitting Multiple Sclerosis

- Relapses and remissions
- Transforms into SPMS
- Attacks of new or increasing neurologic symptoms
- Relapses lead to disability accumulation/EDSS
- RRMS active (with relapses and/or evidence of new MRI activity)
- RRMS not active, worsening (a confirmed increase in disability following a relapse) or not worsening

Secondary Progressive MS

- SPMS follows an initial RRMS
- SPMS a progressive worsening of neurologic function (accumulation of disability) over time
- SPMS active – with relapses and/or evidence of new MRI activity
- SPMS not active, with progression (evidence of disability accumulation over time, with or without relapses or new MRI activity) or without progression

Primary Progressive MS

- PPMS - worsening neurologic function (accumulation of disability) from the onset of symptoms, without early relapses or remissions
- PPMS active (with an occasional relapse and/or evidence of new MRI activity over a specified period of time)
- PPMS not active, with progression (evidence of disability accumulation over time, with or without relapse or new MRI activity) or without progression

Multiple Sclerosis Prognosis

Demographic and environmental factors
- Older age
- Male sex
- Not of European descent
- Low vitamin D levels
- Smoking
- Comorbid conditions

Clinical factors
- Primary progressive disease subtype
- A high relapse rate
- A shorter interval between the first and second relapses
- Brainstem, cerebellar or spinal cord onset
- Poor recovery from the first relapse
- A higher Expanded Disability Status Scale score at diagnosis
- Polysymptomatic onset
- Early cognitive deficits

MRI observations
- A high number of T2 lesions
- A high T2 lesion volume
- The presence of gadolinium-enhancing lesions
- The presence of infratentorial lesions
- The presence of spinal cord lesions
- Whole brain atrophy
- Grey matter atrophy

Biomarkers
- A high number of T2 lesions
- The presence of IgG and IgM oligoclonal bands in the CSF
- High levels of neurofilament light chain in the CSF and serum
- High levels of chitinase in the CSF
- Retinal nerve fibre layer thinning detected with optical coherence tomography

Clinical Case

- 25-year-old Hispanic female
- New onset: weakness of left arm, Numbness
- Medical History: Optic neuritis 3 years ago, depression, smoker
- Current Medications: Vitamin D, partially adherent
- Cultural Considerations: her mother has never heard of the disease
- BRAIN MRI 3 years ago

Courtesy of Aliza Ben-Zacharia, PhD, DNP, ANP-BC, FAAN.
# Meet Criteria?

<table>
<thead>
<tr>
<th>No. of Clinical attacks</th>
<th>No. of MRI lesions with objective clinical evidence</th>
<th>Additional data needed for diagnosis of multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing-remitting multiple sclerosis</td>
<td>≥2</td>
<td>None</td>
</tr>
</tbody>
</table>

| ≥2 | ≥2  | None |

Courtesy of Aliza Ben-Zacharia, PhD, DNP, ANP-BC, FAAN.
Conclusion

- MS is a complex disease with multiple endophenotypes
- High-risk RIS and prodrome may become a part of the MS spectrum in the next version of the McDonald criteria
- Many patients previously labelled as CIS now receive the diagnosis of MS, making the prognosis of both CIS and RRMS milder
- Important to diagnose early and treat early
- Once diagnosed, important to assess the presence of poor prognostic indicators, symptoms, treating exacerbations, starting DMT and managing comorbidities
Thank you!