Multiple Sclerosis
and other Demyelinating Disorders
MHD – Neuroscience Module

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Multiple Sclerosis

What is “Multiple Sclerosis”?
• MS is a presumed autoimmune demyelinating disorder of the central nervous system
• It affects at least 400K Americans (likely greatly underestimated)

Multiple Sclerosis: Early Cases
• Saint Lidwina of Holland was afflicted with a debilitating neurologic disease following a fall at the age of 15 in 1395 characterized by walking difficulties, vision problems, headaches, and facial pain punctuated by periods of remission
  – Fluctuations were attributed to contact with Angels
  – Candlewick was placed around her head with reported recovery of her vision

DON’T MEMORIZE THIS SLIDE. IT IS TO CREATE A HISTORICAL CONTEXT. MULTIPLE SCLEROSIS HAS BEEN AROUND FOR A VERY, VERY LONG TIME.
Multiple Sclerosis: Early Cases

- Well described in the medical literature in the 1800s in case reports and pathology reports
  - Robert Carswell 1838
  - Pathologic Anatomy
- Charcot gets much of the credit for recognizing the disease as a distinct entity
  - Charcot’s Triad (1868): Nystagmus, intention tremor, scanning speech
  - Commented on axonal and demyelinating features and gray matter involvement

Multiple Sclerosis

Who “gets” Multiple Sclerosis?

- Generally (like when you’re taking a test) occurs in younger females (20-50 yo) of Northern European descent
  - Female:male ratio of 2:1 or 3:1
- However…
  - Pediatric MS (~18) may be under-diagnosed (symptoms get better….)
  - Those over 50 incorrectly believed “cannot get it”
  - Those at “lower risk” may be “higher risk” for severe disease

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Who “gets” Multiple Sclerosis?

- Risk seems to increase with distance from the equator
  - May be related to lower Vitamin D levels due to sun exposure (or lack thereof)
  - May acquire that risk early in life (geographic risk established by age 15)
  - However, epidemiologic data is changing for a variety of reasons (population moving south, increased hygiene standards internationally, more MRI scanners)

National Multiple Sclerosis Society: "Kids Camp" for children of parents or caregivers with MS
Multiple Sclerosis

Who “gets” Multiple Sclerosis?

• Genetic contribution but not a “genetic disease”
  – Certain HLA markers and single nucleotide polymorphisms (SNPs) increase risk
  – No genetic or prenatal tests are recommended
  – Lifetime risk of MS: 0.1-0.2%
  – Absolute risk to a child or full sibling: 2-4%
  – Even in identical twins the risk is “only” 25%

“MS clusters with the so-called complex genetic diseases, a group of multifactorial disorders characterized by modest disease risk heritability driven primarily by allelic variants relatively common in the population.” Hauser SL et al. Ann Neurol 2013

Multiple Sclerosis

Who “gets” Multiple Sclerosis?

• Suspected environmental triggers
  – Viral Exposures
    • HBV most commonly implicated in pediatric MS (but high in general)
    • Canine distemper virus (Faroe Islands)
  – Are CMV, HSV and even HIV protective?
  – Tobacco exposure
    • Most doctors think smoking is bad for you…because it is
    • Obesity/dietary factors?
  – Vaccines are safe and do not cause multiple sclerosis.

Hygiene Hypothesis

The relative lack of exposure to infectious agents early in life may lead to defects in immune tolerance. There is some data the parasitic infection may decrease the risk of MS.

Apparently, “rubbing dirt on it” was a good idea…. I do not recommend parasites (yet).

The Cause(s) of Multiple Sclerosis

“MS is caused by bad luck clouds….” – Local MS expert
Pathogenesis of MS

What do we think happens

• Antigen presenting cells (APCs), possibly traveling from the cranial vault, present some signal to & activate primed “autoreactive” T-cells residing within lymph nodes
• Activated T-cells leave the lymph nodes and enter the peripheral blood stream looking for that target (which is presumably “found” in the CNS)

Pathogenesis of MS

What do we think happens

• T cells attach to, break down and cross the blood brain barrier
  – Release interleukins that cause inflammatory response and disrupt the BBB
  – Secret pro-inflammatory cytokines leading to myelin destruction and neuronal death
  – Cell may become “chronically active” within the CNS over time leading to progressive neurodegeneration

Pathogenesis of MS: End Result
Multiple Sclerosis: Impact of Demyelination

- The disease is characterized by clinical relapses (new neurologic signs/symptoms lasting >24 hours) due to CNS demyelination followed by remission (complete or partial improvement in symptoms)
- The frequency of relapses varies but averages one every 1-2 years for the first 5-10 years of the illness after disease onset
- Over time, patients develop progressive symptoms without clear clinical relapses or new lesions

Common classification of MS-subtypes. Most patients (85%) are “relapsing-remitting” at onset. Many develop “secondary progressive” after 1-2 decades.

Clinical Case

- A 23 year old female presents. She reports a few days onset of blurred vision and left eye pain. When she covers her left eye, she can see fine. When she covers her right, she has difficulty seeing the middle of the visual field with the left eye (“it’s like looking through a screen”). You wave a red pen in front of her—it appears “less red” with the left eye. You take out your penlight and shine it into each eye, noting the following on exam:
- Where is the lesion?
**Things to Know for This Case**

1. Light enters the eye and travels back along the optic nerve.
2. Bifurcates at the optic chiasm.
3. Travels along the optic tract to the lateral geniculate.
4. Some fibers bypass the lateral geniculate and pass along the dorsal midbrain targeting the Edinger-Westphal nucleus (CN III).
5. Message to constrict the pupils travels forward along both oculomotor nerves to the pupils.
6. Both pupils constrict.
7. If the optic nerve is "blocked" by inflammation, the message never makes it back and neither eye constricts (Afferent Pupillary Defect or Marcus-Gunn Pupil).

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**Multiple Sclerosis**

**Syndromes Highly Suggestive of MS**

- Optic neuritis (1/5 MS pts)
  - Decreased monocular vision
  - Pain with eye movement
  - Decreased red/green color
  - Clinically associated with an afferent pupillary defect (APD or Marcus-Gunn pupil)
  - Uhthoff phenomenon (heat intolerance)
  - "Hot bath test"

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**Multiple Sclerosis**

**Syndromes Highly Suggestive of MS**

A patient reports double vision when looking left. The following is noted on examination. Where is the lesion?
Things to Know for This Case

- Right frontal eye field initiate plan to look left
- Message is sent the left abducens nucleus/PPRF
- Left abducens nucleus sends a message along the left abducens nerve to the left lateral rectus (abducts the left eye)
- Left abducens/PPRF sends a message up the MLF to the right oculomotor nucleus
- Right oculomotor nucleus sends a message along the right oculomotor nerve to the right medial rectus (adducts the right eye)
- Both eyes turn left at the same time (you cannot move only one eye at a time)

Same concept—I just switched sides so the figures would match: patient with an INO with right gaze (video case was with left gaze).

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Syndromes Highly Suggestive of MS

- Brainstem Syndromes
  - Internuclear ophthalmoplegia
  - Oculomotor dysfunction
  - Ataxia
  - Trigeminal Neuralgia
  - Facial nerve palsy
  - CST/upper motor neuron involvement

CST = corticospinal tract

MS lesions within the periphery of the brainstem. Vascular lesions (strokes) tend to be internal.
Clinical Case

- A 38 year old female presents to the ER. About 2 days ago she noticed that both feet went numb. Symptoms then progressed up her legs into the torso, and then started to involve her hands. When she bends her head forward she gets a sharp shooting pain right down her spine. On examination she has difficulty walking, appearing off-balance. She cannot feel a tuning fork placed against her toes, ankles, knees, hip, lower ribs, or fingers.
- Where is the lesion?

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Syndromes Highly Suggestive of MS

- Spinal Cord Syndrome
  - Partial myelopathy
  - Lhermitte’s “sign” (electric shock sensation with the neck flexed)
  - Numbness/sensory level
  - Deafferented hand
  - Urinary urgency, incontinence, erectile dysfunction (do not occur with GBS—commonly misdiagnosed)
  - Progressive asymmetric spastic paraplegia

PATIENTS WITH A “SENSORY LEVEL” SHOULD BE ASSUMED TO HAVE A SPINAL CORD LESION UNTIL PROVEN OTHERWISE.
Multiple Sclerosis

Treating Relapses (New, Focal Symptoms Due to Inflammation)

- Goal is to speed recovery & limit injury
- Steroids
  - High dose IV methylprednisolone or oral prednisone (if forced to pick on a test, IV steroids are preferred—even though current data suggests IV and PO are equivalent)
  - Typical dose is 1000 mg/day (with no perfect randomized data to support any dose other than “high”)
  - Far and away the most commonly used for acute relapses
- ACTH
- Plasmapheresis
- IV Ig

“Silent” Symptoms of Multiple Sclerosis

- Fatigue 65%-97%
- Bladder dysfunction 52%-97%
- Sexual dysfunction 40%-90%
- Spasticity 40%-85%
- Pain 29%-86%
- Cognitive impairment 40%-70%
- Bowel dysfunction 35%-68%

Multiple Sclerosis

Diagnosis

- “Multiple Sclerosis is what a good clinician would call Multiple Sclerosis”
  
  »Adm. J. Kurtzke
Diagnosis: Schumacher Criteria (1965)

**Six Essential Criteria for “Definite Multiple Sclerosis”**

1. Objective abnormalities on examination; symptoms alone not acceptable
2. Evidence on exam or history of 2 or more separate parts of the CNS
3. Objective evidence must reflect predominantly white matter involvement (fiber tract damage; more than a minor proportion of brainstem findings disqualified pts for studies)
4. Involvement of the neuroaxis must occur temporally:
   - 2 or more episodes of worsening separated by one month or more, each episode lasting at least 24 hrs
   - Slow or step-wise progression of sx’s over a period of 6 months
5. Age 10-50
6. Cannot be better explained by another process

The original criteria, provided to illustrate a point (ie, not to memorize): What’s “missing”?

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Multiple Sclerosis

**Diagnosis: 2017 McDonald Criteria**

- Diagnosis rests on the objective demonstration of CNS white matter lesions—based on clinical and radiographic grounds—that are disseminated in time & space for which there is no better alternative diagnosis
- There is no single test that “confirms” MS—it is ultimately a clinical diagnosis with radiographic corroboration

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**Multiple Sclerosis: Radiographic Diagnosis**

**Dissemination in Space**

- At least one T2 lesion—that is characteristic in appearance for MS—in at least two out of four locations considered characteristic for MS:
  - juxtacortical
  - periventricular
  - infratentorial
  - spinal cord

**Dissemination in Time**

- A new T2 and/or GdE lesion on follow up MRI irrespective of the timing of the baseline MRI
- Can diagnose off of a single MRI
Typical Lesions

MRI Findings

- Juxtacortical
- Periventricular
- Infratentorial
- GdE Lesion

**Typical Lesions**

- Lesions >3mm
- Corpus callosum
- Optic radiation
- Brainstem abutting the 4th ventricle or aqueduct
- Incomplete/partial enhancement
- T1 “Black Holes”

**Dawson’s Finger(s)**

Perpendicular Oriented Periventricular Lesions

Virtually pathognomonic for multiple sclerosis
Multiple Sclerosis

**Spinal Cord Lesions**

- Lesions are typically small (<1-2 vertebral levels)
- Located in the cord periphery, especially the dorsal columns
  - Lesions begin at the pial surface
  - Very few other neurologic diseases (esp stroke) cause discrete spinal cord lesions and brain lesions

Other Tests: Cerebrospinal Fluid

- Cell count <5/mm³
  - Raresly <0.5/mm³
  - Usually 90% lymphocytes and <5% PMN cells
- Protein normal (2/3rds of pts)
  - Rarely >100/mℓ
  - High levels associated with cord swelling
- Glucose normal
  - Rarely >50/mℓ

- Oligoclonal bands (90%-95%) provide evidence for intrathecal synthesis
  - Immunological process in the CNS
  - Once present tend to persist
  - OCCs with optic neuritis or first event (CIS) is associated with an increased risk of MS
- IgG abnormalities common
  - Intrathecal IgG synthesis is highly characteristic
  - Elevated IgG, IgG index or synthesis rate (80%-90%)
  - Not “mandatory” for diagnosis (though some review books think they are)—presence does support a likely immunologically mediated condition

Viral infection (HIV, viral encephalitis, SSPE)
Syphilis
Lyme disease

Differential Diagnosis

- Keep in Mind: Multiple Sclerosis is a common disease of the Central Nervous System that affects discrete areas of White Matter, typically in a relapsing and remitting fashion.
- Big point: consider alternative etiologies, including the following:
Differential Diagnosis

Neuromyelitis Optica
- Longitudinally extensive spinal cord lesion (>3 vertebral segments)
- Bilateral optic neuritis
- Hic-coughs
- Normal/minimal brain lesions (+/-)
- NMO IgG Ab positive

I've done this long enough to know the following is true. Next year one of you is going to work with me on the clerks... I'll ask you, “Have you ever heard of NMO?” and you will say, “No. They never talked about that diagnosis last year”... and a small part of my soul will die.

Acute Disseminated Encephalomyelitis (ADEM)
- Often post-infectious process
- Commonly present with HA, vomiting, drowsiness and meningism (often initially treated for infectious meningoencephalitis)
- Large, “fluffy” multifocal lesions
- More common in children than adults

Multiple Sclerosis

Progressive Multifocal Leukoencephalopathy (PML)
- Opportunistic infection due to the John Cunningham (JC) Virus
  - Commonly seen in the HIV population, including as the initial diagnosis
- Rare (old) side effect that occurs in those on natalizumab (an MS drug) who are also JC Virus positive
- Multiple lesions are commonly present
- Frequently subcortical hemispheric white matter or cerebellar peduncles
- Can lead to death or severe neurologic injury; better chance of recovery with early detection

Hyperintense FLAIR signal in the right middle cerebellar peduncle, classic findings in PML.
Multiple Sclerosis: Treatment Past and Present

“…the whole armoury of the British Pharmacopoeia has been launched against the disease with uniformly disastrous results.”

--Alfred Newman, MD (1875)

Multiple Sclerosis

“There have been more breakthroughs in Multiple Sclerosis than any other disease state in the last decade.”

--Steven Hauser, UCST

There are at least 15 approved therapies for MS with several more expected this year alone.

Multiple Sclerosis

Selecting a Treatment: Considerations

1. Overall Effectiveness
   - Reduction in Relapse Rate
   - Impact on MRI metrics (T2 lesions, enhancing lesions, T1 black holes)
   - Impact on Disability (EDSS)

2. Side Effect Profile
   - Any reason the patient cannot or should not take it?

3. Long Term Safety Profile
   - Usually treating young patients for lengthy periods of time; do we trade today’s problem for tomorrow’s?

4. Will the patient take it?
   - “No medication works less well than the one you don’t take.”

5. The main goal of treatment is to make life as “normal” as possible
   - “I have MS, MS does not have me”
Multiple Sclerosis
Treating Relapses (New, Focal Symptoms Due to Inflammation)

- Goal is to speed recovery & limit injury
- Steroids
  - High dose IV methylprednisolone or oral prednisone (if forced to pick on a test, IV steroids are preferred—even though current data suggests IV and PO are equivalent)
  - Typical dose is 1000 mg/day
  - Far and away the most commonly used for acute relapses
- ACTH
- Plasmapheresis
- IV Ig

First paper to show a positive impact of treatment on MS (1970). That's not going to be tested….how to treat MS relapses is fair game.

Multiple Sclerosis
The Future?

- Glial progenitor cells injected directly into white matter pathways induce myelin growth in genetically altered “shaker mice”
- Mice then live relatively normal neurologic mouse lives
- Phase I study launched in 2014
- HSCs have shown promise in early aggressive MS

Multiple Sclerosis
The Future?

- to cure: a means of healing or restoring to health
  - Ocrelizumab: anti-CD20 monoclonal antibody given every 6 months; 89-95% reduction in new lesions, 73-80% reduction relapses
  - If a patient never has another lesion, and never has another relapse, will they never get worse? Is that “a cure”? 
  - 3 Tesla using T2* for better diagnosis
  - Neurofilament Light Chain to assess response to therapy
Multiple Sclerosis

Key Points

1. Multiple sclerosis is a demyelinating disorder of the central nervous system
2. The diagnosis should be suspected based off of clinical symptoms
3. MRI is helpful in confirming the diagnosis….but does not take the place of your clinical suspicion
4. There are increasingly, and increasingly effective, treatment options for MS

Multiple Sclerosis DMTs

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Betaseron (IFN β1b) SC QOD</td>
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<tr>
<td>1996</td>
<td>Avonex (IFN β1a) IM Qweek</td>
</tr>
<tr>
<td>1997</td>
<td>Copaxone (GA) SC QDaily</td>
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<tr>
<td>2001</td>
<td>Rebif (IFN β1a) SC 3x’s/week</td>
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### Multiple Sclerosis

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<tr>
<th>Year</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>2004</td>
<td>Tysabri (Natalizumab) IV QMonth</td>
</tr>
<tr>
<td>2010</td>
<td>Gilenya (FTY) PO QDaily</td>
</tr>
<tr>
<td>2012</td>
<td>Aubagio (Teriflun) PO Qdaily</td>
</tr>
<tr>
<td>2013</td>
<td>Tecfidera (DMF) PO Qdaily</td>
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<tr>
<td>2014</td>
<td>Lemtrada (Alemtuzumab) IV Yearly</td>
</tr>
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### Multiple Sclerosis

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>2016</td>
<td>Daclizumab SC QMonth</td>
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<tr>
<td>2017</td>
<td>Ocrelizumab IV 2x’s/year</td>
</tr>
<tr>
<td>2019</td>
<td>Cladribine</td>
</tr>
<tr>
<td>2019</td>
<td>Siponimod</td>
</tr>
<tr>
<td>2018?</td>
<td>Anti-LINGO (remyelination)</td>
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The challenge is no longer the lack of effective treatments. The challenge is in navigating the increasingly complex and effective therapy options.