Agenda

• Overview of MS: Demographics, Societal Impact
• Immunopathology, MRI findings
• Disease Patterns
• Presenting Symptoms/work-up
• MS medication overview
  – Increasing importance of MOA
• Important side effects
• Weighing risks vs benefits
• Auto-immune disease affecting the CNS
• 400,000+ patients in North America
  – 2.3 Million patients worldwide
• Women:Men 3:1
• Usual age at diagnosis: 20-40
• Increased incidence in populations farthest from the equator; very high in the NW
  – Role of Vitamin D
MS Risk Factors

- Convergence of multiple risk factors, including
  - **Genetics**: Northern European Ancestry
    - Multiple genetic factors have been discovered since mapping of the Human Genome
      - HLA-DR2, IL-2R, IL-7Ra
    - Fam Hx increases risk 5-10X; 25% concordance for identical twins, 1-2% for non-identical twins
  - **Environment**: Vitamin D deficiency, smoking
  - **Triggers**: infectious exposure prior to age 15
    - HV6? Chlamydia? EBV?
• A leading cause of physical disability in patients under 50
• Most common cause of dementia under 50
• Fatigue, cognitive deficits lead many patients to leave the workforce
• Higher incidence of divorce
Immunopathology

A adapted from Miller et al: Continuum: Multiple Sclerosis (Part A): 1999:5-7
Immunopathology

1. Immune cells pass through blood-brain barrier
2. Immune cells may reactivate and produce cytokines
3. Immune cells stimulate autoimmune attack against myelin

Systemic Circulation

Blood-Brain Barrier

Central Nervous System
“Classic” MS lesions

- **Shape/Size**: Globular, >3mm
- **Location**: Peri-ventricular, juxtacortical, infratentorial
- **Orientation**: lesions aligned along the veins, radiating out from the center (“Dawson’s Fingers”)
MS MRI Findings

FLAIR Axial image

T1 +Gd Axial image
MS MRI imaging

T2 Sagittal image

T1 Gd+ Sagittal image
MS Disease Patterns

- Relapsing-Remitting
  - 85% of patients
- Secondary Progressive
- Primary Progressive
- Progressive-Relapsing
## Presenting Symptoms

<table>
<thead>
<tr>
<th>MS Lesion Location</th>
<th>Patient Symptom (developing over hours to days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic Nerve “Optic Neuritis”</td>
<td>Painful monocular visual loss Loss of red perception Scotoma in visual field, APD</td>
</tr>
<tr>
<td>Brainstem or Cerebellum</td>
<td>Any of the following: Diplopia, facial numbness/pain, dysarthria, dysphagia, ataxia</td>
</tr>
<tr>
<td>Pyramidal Tract: Subcortical to motor strip, internal capsule, cerebral peduncle</td>
<td>Contralateral Hemiparesis, including face, arm, and leg</td>
</tr>
<tr>
<td>Spinal Cord:”Transverse Myelitis” (dorsal columns, lateral columns, spinothalamic tracts)</td>
<td>Dysesthesias bilaterally below the level of the lesion, pseudo-ataxia, symmetric limb weakness, bladder/bowel dysfunction, L’Hermitte’s sign</td>
</tr>
</tbody>
</table>
MS mimics

• Many diseases can mimic MS lesions on MRI
  – Microvascular disease or small embolic CVAs
  – Migraine
  – Normal aging

• MRI lesion patterns for non-MS conditions:
  – Small, round, punctate (3mm or less)
  – Scattered in parietal lobes
Work-up

- Given a suggestive history, consider labs for:
  - Rheumatologic conditions
    - ANA, ACE, SS-A, SS-B
  - Infectious Diseases
    - HIV, Lyme
  - Hypercoagulation
    - aPL, ? “stroke in the young” work-up
  - Neoplastic: Lymphoma
  - Metabolic (myelopathy): B12, MMA, copper
Work-up: CSF

• Usual CSF orders for MS suspected patients:
  – Glucose, Protein, Cell count with diff
  – IgG Index, CSF Protein Electrophoresis
    • Shows Oligoclonal Bands in 85+% of patients
  – Depending on clinical suspicion:
    • CSF culture, Lyme, cytology, CSF ACE
# Diagnostic Criteria

## 2010 McDonald Criteria

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Information Needed for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more separate clinical attacks, affecting 2 or more CNS regions (dissemination in time and space)</td>
<td>No additional data needed; dx confirmed clinically</td>
</tr>
<tr>
<td>2 or more attacks, but only 1 physical finding on exam (dissemination in time)</td>
<td>Show damage accumulation in “space” with : 1. a separate MRI lesion or 2. a separate clinical attack</td>
</tr>
<tr>
<td>1 attack, but physical exam shows 2 CNS regions involved (dissemination in space)</td>
<td>Show accumulation of damage over time with 1. new MRI lesion or 2. new clinical attack</td>
</tr>
<tr>
<td>1 attack and physical exam showing only 1 CNS region involved (“CIS”)</td>
<td>Show accumulation over “space” and “time” with 1. new attack in a new CNS region or 2. MRI with old/new lesions in multiple locations</td>
</tr>
</tbody>
</table>
MS MEDICATIONS
Multiple New Therapies

• MS treatment options have dramatically expanded, most arriving since 2010
• Differing Routes of Administration
  — Previously injectable, now also oral and IV
• Most have unique MOA
• Increasing efficacy brings increasing risk of rare but potentially deadly side effects
Injectable Therapies

<table>
<thead>
<tr>
<th>MS Treatment “Platform Therapies”</th>
<th>Year Approved</th>
<th>Form of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interferons</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaseron (IFN β-1b)</td>
<td>1993</td>
<td>s.c. qOD</td>
</tr>
<tr>
<td>Avonex (IFN β-1a)</td>
<td>1996</td>
<td>IM weekly</td>
</tr>
<tr>
<td>Rebif (IFN β-1a)</td>
<td>2002</td>
<td>s.c. TIW</td>
</tr>
<tr>
<td>Extavia (IFN β-1b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plegridy (PEGIFN β-1a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2009</td>
<td>s.c. qOD</td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>s.c. bi-weekly</td>
</tr>
<tr>
<td><strong>Glatiramer Acetate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copaxone 20mg</td>
<td>1997</td>
<td>s.c. daily</td>
</tr>
<tr>
<td>Copaxone 40mg</td>
<td>2014</td>
<td>s.c. TIW</td>
</tr>
<tr>
<td>Glatopa 20mg</td>
<td>2015</td>
<td>s.c. daily</td>
</tr>
<tr>
<td>Generic GA 20, 40mg</td>
<td>2017</td>
<td>s.c. daily/TIW</td>
</tr>
</tbody>
</table>
## Oral Therapies

<table>
<thead>
<tr>
<th>MS Treatment “Oral Therapies”</th>
<th>Year Approved</th>
<th>Form of Administration and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilenya (fingolimod)</td>
<td>2010</td>
<td>Oral, 0.5mg daily</td>
</tr>
<tr>
<td>Aubagio (teriflunomide)</td>
<td>2012</td>
<td>Oral, 14 or 7mg daily</td>
</tr>
<tr>
<td>Tecfidera (dimethyl fumarate)</td>
<td>2013</td>
<td>Oral, 240mg BID</td>
</tr>
<tr>
<td>MS Treatment “Infusion Therapies” (monoclonal antibody)</td>
<td>Year Approved</td>
<td>Form of Administration, Dose</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>---------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Tysabri (natalizumab)</td>
<td>2007</td>
<td>IV, 300mg every 28 days</td>
</tr>
<tr>
<td>Lemtrada (alemtuzumab)</td>
<td>2012</td>
<td>IV, 12mg/day x5 year 1, then 12mg/day x 3 year 2</td>
</tr>
<tr>
<td>Ocrevus (ocrelizumab)</td>
<td>2017</td>
<td>IV, 300mg on day 1&amp;14, then 600mg q6 months</td>
</tr>
</tbody>
</table>

*FDA approved for RRMS & PPMS*
MOA Strategies

Prevent production of pro-inflammatory cells
Reduce Activation or destroy activated cells
Prevent entry into the CNS
## Preventing Production

<table>
<thead>
<tr>
<th>MS Treatment</th>
<th>MOA</th>
<th>Notable side effects</th>
<th>Pre-admin work-up</th>
<th>Ongoing monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Copaxone</strong></td>
<td>Th1 to Th2 shift</td>
<td>Site rxn lipoatrophy “systemic” reaction</td>
<td>None required</td>
<td>None required</td>
</tr>
<tr>
<td>Glatiramer Acetate</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Aubagio</strong></td>
<td>Blocks DHODH, needed for activated T and B cell proliferation</td>
<td>GI, rash, alopecia, increased BP, elevated LFTs, pregnancy risk</td>
<td>CBC, CMP, Quantiferon</td>
<td>LFTs monthly x 6, periodic CBCs</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td></td>
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</tr>
</tbody>
</table>
## Depleting B or T cells

<table>
<thead>
<tr>
<th>MS Treatment</th>
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<th>Ongoing monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocrevus ocrelizumab</td>
<td>Binds to CD20; depletes mid-life cycle B-cells</td>
<td>Infusion Reactions, infections</td>
<td>CBC, LFTs, Hepatitis B</td>
<td>None required</td>
</tr>
<tr>
<td>Lemtrada alemtuzumab</td>
<td>Binds to CD52 depleting most B and some T cells</td>
<td>IRRs, long-term auto-immunity</td>
<td>CBC, LFTs, Quantiferon</td>
<td>LFTs, CBC monthly; UA, TSH</td>
</tr>
</tbody>
</table>
# Reducing T-cell Activation

<table>
<thead>
<tr>
<th>MS Treatment</th>
<th>MOA</th>
<th>Notable side effects</th>
<th>Pre-admin work-up</th>
<th>Ongoing monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zinbryta</strong></td>
<td>Antibody blocks IL-2 cytokine receptor,</td>
<td>Site reactions, <em>abnormal LFTs/bili, skin rashes</em></td>
<td>CBC, LFTs, Hepatitis B</td>
<td>Monthly LFTs</td>
</tr>
<tr>
<td><strong>daclizumab</strong></td>
<td>preventing T-cell activation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Blocking T-cell Trafficking

<table>
<thead>
<tr>
<th>MS Treatment</th>
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<th>Notable side effects</th>
<th>Pre-admin work-up</th>
<th>Ongoing monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tysabri</strong> natalizumab</td>
<td>Blocks T-cell entry through the Blood-Brain Barrier</td>
<td>IRRs, LFT; elevations, <em>HA and joint aches</em>, infections, <em>high PML risk &gt;2yrs</em></td>
<td>CBC, LFTs, JCV titer</td>
<td>CBC, LFTs, JCV titer every 6 months</td>
</tr>
<tr>
<td><strong>Gilenya</strong> fingolimod</td>
<td>Prevents T cell egress from Lymph nodes</td>
<td><em>Lymphopenia</em>, abnormal LFTs,infections, <em>bradycardia, macular edema, PML</em></td>
<td>CBC, LFTs, Quantiferon, VZV, Derm survey, ophtho exam, EKG, First dose monitoring</td>
<td>LFTs, CBC, eye exam 3 months after tx, BP monitoring</td>
</tr>
</tbody>
</table>
### MOA multi-modal or other

<table>
<thead>
<tr>
<th>MS Treatment</th>
<th>MOA</th>
<th>Notable side effects</th>
<th>Pre-admin work-up</th>
<th>Ongoing monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferons INF β-1a, INF β-1b</td>
<td>Shifts cytokine balance to anti-inflammatory; reduces T cell trafficking</td>
<td>Site reactions, flu-like AEs, leukopenia, elevated LFTs, depression, suicidality</td>
<td>CBC, LFTs, Hepatitis B</td>
<td>CBC, LFTs</td>
</tr>
<tr>
<td>Tecfidera Dimethyl fumarate</td>
<td>Activates Nrf2 pathway (reduces oxidative stress)</td>
<td>GI side effects, flushing, Lymphopenia, infex, PML</td>
<td>CBC, LFTs</td>
<td>LFTs, CBC</td>
</tr>
</tbody>
</table>
MEDICATION CHOICE: WEIGHING RISK VS BENEFIT
Weighing Risk vs Benefit

- High efficacy, low risk
- High efficacy, high risk
- Low efficacy, low risk
- Low efficacy, high risk
Efficacy vs Risk

- Copaxone
- Glatiramer Acetate
- Interferons
- Aubagio
teriflunomide
- Tecfidera
- DMF
- Zinbryta
daclizumab
- Gilenya
fingolimod
- Ocrevus
ocrelizumab
- Tysabri JCV+
natalizumab
- Lemtrada
alemuzumab
- Zinbryta
- daclizumab
- Gilenya
- fingolimod
- Tecfidera
- DMF
- Aubagio
teriflunomide
- Interferons
- Copaxone
Glatiramer Acetate

Efficacy vs Risk
Individualizing Treatment

Many factors influence final DMT choice

- Disease Severity
- Patient Co-morbidities
- Patient Risk Tolerance
- Medication Reversibility
- Medication Risk
Summary

- MS is an autoimmune CNS disease affecting women > men, with potential for severe disability if not treated early
- Clues to the dx can be found in sx patterns, MRI lesion types
- MS mimicking diseases need to be ruled out
- MS medication overview/side effects
- Weighing risks vs benefits of 13+ medications
Implications for Primary Care

• You are on the “front line” for MS first symptoms: keep vigilant for typical sx patterns!
• Watch out for medication side effects
  — Infections, rising LFTs, lymphopenia, HTN
• Patients with MS are at risk for other autoimmune diseases
• Good overall health is critical to keeping MS patients functioning at their best capacity
QUESTIONS?