Updates in Multiple Sclerosis

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Goals

• Review the basic pathophysiology, course, and treatment of multiple sclerosis
• Specific focus on early forms of disease
  • So called ‘radiographically-isolated syndrome’ and clinically-isolated syndrome
• Role of newer, and generally more efficacious treatments
• Review of JC virus, progressive multifocal leukoencephalopathy (PML), and the risk in our medications
Review of Multiple Sclerosis
What is Multiple Sclerosis?

• A demyelinating disease causing relapses of focal neurological dysfunction, most commonly with improvement or resolution of symptoms
• Progressive disease develops in a minority of patients
• A common cause of neurological disability in young adults
• One of the most treatable neurological conditions
Multiple Sclerosis Typical MRI
Risk factors

- HLA DRB*1501 is the best established genetic risk factor
- Family history (up to ~20% for twins, 1-3% with affected sibling, 2-3% with affected parent)
- Low vitamin D levels
- High latitude for first 16 years of life*

Epidemiology of MS

Epidemiology of MS

- Recent studies suggest latitude gradient is less clear
- US Prevalence is now estimated at > 200 per 100,000
  - ~1 million patients with MS in the US
- Suggestion that African Americans, particularly women, are more frequently affected than previous estimates


# Diagnosis of MS

- The diagnosis is based on dissemination in *time* and *space*

<table>
<thead>
<tr>
<th>Number of lesions with objective clinical evidence</th>
<th>Additional data needed for a diagnosis of multiple sclerosis</th>
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<tbody>
<tr>
<td>≥2 clinical attacks</td>
<td>None*</td>
</tr>
<tr>
<td>≥2 clinical attacks (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)</td>
<td>None*</td>
</tr>
<tr>
<td>≥2 clinical attacks</td>
<td>Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site by MRI‡</td>
</tr>
<tr>
<td>1 clinical attack</td>
<td>Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶</td>
</tr>
<tr>
<td>≥2</td>
<td>Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶</td>
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</tbody>
</table>

Diagnosis of MS

• Practically, we use MRI, CSF, and clinical information to make the diagnosis
• Patients are seen frequently early on, with serial imaging to allow for an expedited diagnosis and treatment
Diagnosis of MS

- Misdiagnosis remains a large issue
- MS referrals to subspecialists accurate 30% of the time
  - Usually based on MRI findings
- Alternative etiologies: migraine, hypertensive changes, psychiatric illness, pain disorders
- A single diagnosis code for MS has low sensitivity and specificity for a true diagnosis


Early Forms of Disease
Radiographically isolated syndrome (RIS)

- Used to describe MS typical lesions in a patient with no attacks and normal exam
- Not a formal diagnosis
- Proposed criteria:
  - MS-like lesions in 3 of 4 typical areas (juxtacortical, periventricular, brainstem, and spinal cord)
  - Not a vascular pattern
  - No clinical symptoms or localizing exam findings
  - Not substance-related
  - Other processes excluded

Radiographically isolated syndrome (RIS)

Compare and Contrast

Radiographically isolated syndrome (RIS)

- Risk of conversion to a clinical syndrome at 5 years:
  - 34%
- Predictors of conversion:
  - Male sex
  - Age < 37 years
  - Spinal cord lesions

Clinically Isolated Syndrome (CIS)

- MS-like clinical presentation that either lacks dissemination in *time* or *space*
- Typical clinical syndromes:
  - **Optic neuritis**, focal supratentorial syndrome, **focal brainstem syndrome**, partial myelopathy
- With our new criteria, less patients will have clinically isolated syndrome
  - Easier to make diagnosis of MS
  - MRI can provide time and space
  - Positive CSF can provide time
Clinically Isolated Syndrome (CIS)

- How much of CIS is ultimately MS?
  - In the largest analysis to date, 72% met criteria for a diagnosis of multiple sclerosis over a median of ~ 7 years
  - MRI findings were the greatest predictor
- Can we delay or prevent the onset of MS with treatment?
  - Possibly
  - 3 medications have been studied in CIS in clinical trials

Clinically Isolated Syndrome (CIS)

- **Interferon beta-1a**
  - Various formulations employed
  - Reduced risk of progression to MS by 40-50% over 2-3 years
- **Glatiramer acetate**
  - Reduced risk of progression to MS by 45% over roughly 3 years
- **Teriflunomide**
  - Reduced risk of progression to MS by ~40% over roughly 2 years


Evolution of treatment
Evolution of treatment

- Betaseron 1993 (interferon beta-1b)
- Avonex 1996 (interferon beta-1a)
- Copaxone 1997 (glatiramer acetate)
- Novantrone 2000 (mitoxantrone)
- Rebif 2002 (interferon beta-1a)
- Tysabri 2006 (natalizumab)
- Extavia 2009 (interferon beta-1b)
- Gilenya 2010 (fingolimod)
- Aubagio 2012 (teriflunomide)
- Tecfidera 2013 (dimethyl fumarate)
- Plegridy 2014 (peginterferon beta-1a)
- Lemtrada 2014 (alemtuzumab)
- Glatopa 2015 (generic glatiramer acetate)
- Zinbryta 2016 (daclizumab)
- Ocrevus 2017 (ocrelizumab)*
Evolution of treatment

Approach to therapy

• ‘Escalation’ versus ‘Induction’
  • Two groups, one favoring highly effective medication early, one escalating therapy if breakthrough disease occurs early
  • Data is growing for use of highly effective medications early
  • Definition of aggressive disease is somewhat opaque
    • Most physicians would consider 2 or more relapses a year ‘aggressive’
  • Our goal is to obtain ‘NEDA’, or no evidence of disease activity.
    • No relapses, no new lesions on MRI, and no increase in disability
Natalizumab

- Humanized antibody to a4 integrins, prevents lymphocytes from crossing blood-brain barrier
- Highly effective in reducing multiple pertinent outcome measures.
- May have some benefit in secondary progressive disease
- Dosed at 300mg every 4 weeks, although alternative regimens are employed
- Side effects: PML

**Alemtuzumab**

- Humanized monoclonal antibody versus CD52, a marker widely expressed on leukocytes
- Highly effective in multiple outcome measures, both clinical and radiographic
- Given as two short courses of therapy one-year apart, referred to as ‘interrupted immunotherapy’
- **Side effects:** Autoimmune disease (*thyroid disease*, ITP, glomerulonephropathy), infections (*listeria*, *herpes-related*), serious infusion reactions.

Ocrelizumab

- Humanized monoclonal antibody versus CD20, a marker of a wide lineage of B cells
- Effective for relapsing-remitting and **primary progressive MS**
  - Reduces relapses by ~50% compared to interferon beta-1a
  - Reduces risk of disability progression in PPMS by 25%
- Dosed every 6 months (first dose split over two weeks)
- **Side effects:** increased URIs, herpetic infections, possible increase in serious infections, PML, and cancer*

PML risk in MS Medications
Risk of progressive multifocal leukoencephalopathy (PML)

- What is PML?
  - Caused by JC virus, a DNA virus ubiquitous in the environment
  - 60% of the population is exposed
  - Rarely causes disease in immunocompetent hosts, best described in patients with AIDS
  - Risk in MS was first discovered in trials of natalizumab with multiple sclerosis
  - No proven effective treatment (treat immunosuppressive condition and supportive care)
Progressive Multifocal Leukoencephalopathy in a Patient Treated with Natalizumab

Annette Langer-Gould, M.D., Scott W. Atlas, M.D., Ari J. Green, M.D., Andrew W. Bollen, M.D., and Daniel Pelletier, M.D.

Progressive Multifocal Leukoencephalopathy after Natalizumab Therapy for Crohn's Disease

Gert Van Assche, M.D., Ph.D., Marc Van Ranst, M.D., Ph.D., S. Sciot, M.D., Ph.D., Benedicte Dubois, M.D., Ph.D., Séverine Vermeire, M.D., Ph.D., Maja Noman, M.D., Janvick Verbeeck, M.Sc., Karel Geboes, M.D., Ph.D., Wim Robberecht, M.D., Ph.D., and Paul Rutgeerts, M.D., Ph.D.

Progressive Multifocal Leukoencephalopathy Complicating Treatment with Natalizumab and Interferon Beta-1a for Multiple Sclerosis

B.K. Kleinschmidt-DeMasters, M.D., and Kenneth L. Tyler, M.D.

Risk of PML in MS Medications

• A risk of PML has now been seen in multiple medications
  • Gilenya (fingolimod)
    • ~20 cases, <1/10000 risk
    • Risk factors not clearly established, many older patients
  • Tecfidera (dimethyl fumarate)
    • <10 cases, <1/10000 risk
    • Possible risks of decreased lymphocyte counts (ALC < 500), older age
  • Natalizumab
    • Risk stratification possible
Risk of PML in Natalizumab

- A viral titer assay was developed as part of the REMS program
- Titer is checked every 6 months (some centers every 3 months)
- Allows for a stratification of risk
  - Negative or low-titer = low risk
  - Medium-high titer and > 24 months of exposure = high risk
  - Prior immunosuppression increases risk, and is a relative contraindication
## Risk of PML in Natalizumab

<table>
<thead>
<tr>
<th>PML risk estimate (per 1000)*</th>
<th>Monitoring steps</th>
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<tbody>
<tr>
<td></td>
<td>Anti-JCV antibody</td>
</tr>
<tr>
<td><em>Immunomodulatory drug treatment, including natalizumab</em></td>
<td>--</td>
</tr>
<tr>
<td><em>Natalizumab treatment, anti-JCV negative</em></td>
<td>--</td>
</tr>
<tr>
<td><em>Natalizumab treatment, anti-JCV positive, no prior immunosuppression</em></td>
<td></td>
</tr>
<tr>
<td>Anti-JCV antibody index &lt;0.9</td>
<td>Treatment duration 1-72 months</td>
</tr>
<tr>
<td>Anti-JCV antibody index 0.9-1.5</td>
<td>Treatment duration 1-36 months</td>
</tr>
<tr>
<td>Treatment duration 37-72 months</td>
<td>2-3</td>
</tr>
<tr>
<td>Anti-JCV antibody index &gt;1.5</td>
<td>Treatment duration 1-24 months</td>
</tr>
<tr>
<td>Treatment duration 25-72 months</td>
<td>3-10</td>
</tr>
<tr>
<td><em>Natalizumab treatment, anti-JCV positive, prior immunosuppression</em></td>
<td></td>
</tr>
<tr>
<td>Treatment duration 1-24 months</td>
<td>0-3-0.4</td>
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<tr>
<td>Treatment duration 25-72 months</td>
<td>4-8</td>
</tr>
</tbody>
</table>

Management of PML in Natalizumab

• Care is generally supportive
• Many practitioners will employ plasma exchange to remove circulating natalizumab, but this is not proven helpful
• A positive note:
  • Introduction of a JC virus monitoring protocol in Sweden led to total prevention of natalizumab-associated PML (2012-present)

Kagstrom, S. et al. Reduction of the risk of PML in natalizumab treated MS patients in Sweden: an effect of JCV ab index surveillance (MULTIPLE SCLEROSIS JOURNAL, 2018)
Questions?