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Diagnosis and Treatment Options for Multiple Sclerosis

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Diagnosis and Treatment Options for MS

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History of MS

- Thought to be immune mediated
  - Virally triggered in genetically susceptible host

- Treatments
  - Acute attacks: ACTH in 1970s–1980s
  - Disease modification in 1990s
  - Symptomatic management

- Diagnostic tests
  - MRI in 1980s
  - New MRI techniques
What We Know Now...

- Most common neurological disease of young adults
- Chronic disease of the CNS
  - Inflammation, demyelination, axonal degeneration
- Approximately 350,000 cases in US
- 2/3 of MS patients are women
- Associated with Northern European ancestry
- Age of onset: 15–55
  - Usually diagnosed in 20s–30s
Statistics

■ Worldwide distribution
  - High prevalence 30+/100,000
    • Northern US and Canada
    • Most of Europe
    • Southern Australia
    • New Zealand
    • Northeast Russia
Pathology

- White matter lesions in CNS
  - Surrounded by plasma cells, immunoglobulins, macrophages, and lymphocytes

- Grey Matter
  - Cortex, Basal Ganglia

- Inflammation
  - Myelin injury and destruction
  - Axonal injury and destruction
Demyelination and Axonal Transection

Disease Course

- 85%–90% of patients present with a RR pattern of neurological symptoms

- 10%–15% never have relapses (PP)

- Historically - After approximately 10 years, nearly 50% of RR patients will show a progressive pattern to their disease
  - This percentage grows with time
  - Now believed longer than 10 years due to earlier treatment
Disease Courses in MS

- **RRMS**
- **SPMS**
- **PPMS**
- **PRMS**

Natural History Over Time

Disease Type at Diagnosis
- RRMS: 85%
- PPMS: 15%

Disease Type at 11–15 Years After Diagnosis (Among Those With RRMS at Diagnosis)
- SPMS: 42%
- RRMS: 58%
Symptoms vary widely in incidence and severity.

Symptoms:
- Fatigue
- Sensory disturbances
- Visual disturbances
- Elimination dysfunction
- Gait Disturbances
- Spasticity
- Pain
- Tremor
- Cognitive
Diagnosis of MS

- Basic principles
  - Demographic profile
    - Female, Caucasian, young adult
  - Clinical presentation
    - Symptomatic disease, Abnormal exam
    - Flare or attack = 24 hours – up to 3 or more weeks
  - Laboratory profile
    - MRI
    - CSF
    - Evoked potentials
    - Exclusion of other diagnoses
MS - Clinical Presentation

- Sensory tracts
  - 21%–55% of patients
  - Most common presenting symptom
    - Tingling, burning, “Novocaine-like,” band-like, squeezing
    - Lhermitte’s
    - Neuritic pain
    - Exam - Diminished vibratory sensation
    - Exam - Impaired position sense
    - “Useless hand” syndrome
      - Sensory loss, loss of position sense
      - Mobility preserved
Corticospinal tracts

- 32%–41% of patients
  - Heaviness, weakness
  - Abnormal DTRs
  - Positive Babinski response
  - Spastic limb weakness
MS - Clinical Presentation

- **Brainstem**
  - **Eye movement abnormalities**
    - Diplopia at onset in about 7% of patients
    - Nystagmus, INO
    - Bilateral INO is almost pathognomonic for MS
  - **Vertigo**
  - **Infrequently**
    - Dysarthria
    - Peripheral 7th
    - Hearing loss and tinnitus
MS - Clinical Presentation

**Visual pathway**

- **Optic neuritis**
  - Presenting symptom in up to 25% of patients
  - Dimming or visual loss
  - Loss of color vision
  - Visual field defect

**Cerebellar**

- Gait ataxia, limb ataxia, tremor
MS - Clinical Presentation

- Fatigue
  - Present in up to 90% of patients with long-term MS
  - Can be seen with any Flare/Attack

- “Elimination” brainstem/spinal cord
  - Occasionally present at onset of disease
  - Bladder urgency, frequency, hesitation, nocturia
  - Bowel constipation, infrequently involuntary bowel movements
MS Diagnosis

- Posner Criteria (1983)
  - Two clinical attacks in Space and Time
  - No other explanation
  - Paraclinical Evidence (VEP and CSF)
    - MRI not available

- McDonald Criteria 2001
- McDonald Criteria revised in 2005
- McDonald Criteria revised in 2010
McDonald Diagnostic Criteria

- Preserve traditional diagnostic criteria of 2 attacks of disease separated in space and time
  - Must be no better explanation
  - Add specific MRI criteria, CSF findings, and analysis of evoked potentials as means of identifying the second “attack”

- Conclude that the outcome of the diagnostic workup should yield 1 of 3 outcomes:
  - MS
  - Possible MS
  - Not MS
McDonald MRI Criteria - 2005

Abnormal MRI consistent with MS defined as:

- Must have at least 3 of the following:
  - 1 gadolinium-enhancing lesion or 9 hyperintense lesions if no gadolinium-enhancing lesion
  - 1 or more infratentorial lesions
  - 1 or more juxtacortical lesions
  - 3 or more periventricular lesions
    - 1 cord lesion = 1 brain lesion
McDonald MRI Criteria

- Gd-enhancing
- T2 hyperintense
- Infratentorial
- Juxtacortical
- Periventricular
- Spinal Cord
2010 Revised McDonald MRI Criteria

- Abnormal MRI consistent with MS defined as:
  - **Dissemination in Space**
    - >= 1 lesion at least 2 of the 4 characteristic areas: Periventricular, juxtacortical, infratentorial, spinal cord
  - **Dissemination in Time**
    - Enhancing and Non-Enhancing lesions
    - New Lesion
    - New Clinical Attack

** LP and other Ancillary tests not required if no other explanation and above clearly seen

** Can make diagnosis with single attack/first MRI
McDonald MRI Criteria

Gd-enhancing

T2 hyperintense

Infratentorial

Juxtacortical

Periventricular

Spinal Cord
Other Paraclinical Evidence

- Abnormal CSF
  - Oligoclonal IgG bands in CSF and not in serum
  - Or elevated IgG index

- Abnormal evoked potentials (VER, SSEP)
  - Delayed but well-preserved waveform
Differential Diagnosis

- **Infection**
  - Lyme, syphilis, PML, HIV, HTLV-1

- **Inflammatory**
  - SLE
  - Sjögren’s, vasculitis, sarcoidosis, Behçet’s disease

- **Metabolic**
  - $B_{12}$ deficiency, rare familial diseases

- **CNS lymphoma**
- **Degenerative spinal disease**
- **Motor neuron disease**
Serum Testing

- B₁₂, folate
- RPR, FTA
- HIV
- HTLV-1
- ANA, SS-A, SS-B
- Antiphospholipid antibodies
- ESR, C-reactive protein
- Thyroid function
- Angiotension-converting enzyme
- Anti-acetylcholine receptor antibodies
- Long-chain fatty acids
MRI in MS

- MRI Brain
  - Classic Lesions = 90%–95% sensitivity/specificity
  - Newer data on Grey Matter Lesions
  - Brain Atrophy

- MRI Spinal Cord
  - Lesions seen in 50%–75% of cases
    - <= 1-2 vertebral levels
    - >= 3 continuous lesions – think NeuroMyelitis Optica
T1-Weighted Images
T1 Hypointensities

- “Black holes”
  - Thought to be areas of axonal loss
  - Can be “black holes” that are temporary with a new lesion

- Black holes not associated with a new lesion are thought to be areas of permanent damage
T1 Black Holes
T2-Weighted Images

Conventional T2

FLAIR
FLAIR Image
FLAIR Image and T1 Black Holes
Spinal MRI in MS

- Spinal cord lesions in 75% of MS patients
- Predominantly in C-spine
- Usually dorsolateral or central and 0.5 cm by 1–2 cm, and 1–2 vertebral segments
- Less likely to enhance or cause cord swelling
- More likely to cause progressive disease
- T2 less predictive of disability than atrophy
Cord Lesion
Examples of BPF in MS

MS Diagnosis

- Two “other” Categories
  - Clinically Isolated Syndrome
    - First Clinical Attack
    - MRI with 1 or 2 lesions
  - Radiological Isolated Syndrome
    - MRI with “Classic” MS lesions
    - No clinical history
      ** VEP, Cervical Spine, +/- LP
Radiological Evidence

- Natural history studies demonstrate that up to 88% of patients with 1 attack and MRI lesions go on to convert to CDMS.\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Study</th>
<th>Normal MRI</th>
<th>Abnormal MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brex et al.</td>
<td>19%</td>
<td>88%</td>
</tr>
<tr>
<td>Optic Neuritis Study Group (final follow-up–15 y)\textsuperscript{3}</td>
<td>25%</td>
<td>72%</td>
</tr>
<tr>
<td>Minneboo et al.</td>
<td>24%</td>
<td>72%</td>
</tr>
<tr>
<td>Tintore et al.</td>
<td>8%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Development of CDMS, stratified for baseline MRI findings. Modified from Miller et al.

CDMS = clinically definite multiple sclerosis.
## Relationship Between No. of T2 Lesions at Baseline and Clinical Outcome by 20 Years in CIS Patients

### 20-Year Follow-Up of Prospectively Recruited CIS Cohort

<table>
<thead>
<tr>
<th>Baseline Lesions</th>
<th>CDMS at 20 yrs</th>
<th>EDSS &gt;3 at 20 yrs</th>
<th>EDSS ≥6 at 20 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n = 34)</td>
<td>7 (21%)</td>
<td>9 (26%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>1-3 (n = 22)</td>
<td>18 (82%)</td>
<td>8 (36%)</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>4-9 (n = 20)</td>
<td>17 (85%)</td>
<td>10 (50%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>10+ (n = 31)</td>
<td>25 (81%)</td>
<td>20 (65%)</td>
<td>14 (45%)</td>
</tr>
</tbody>
</table>

Proposed Algorithm for Evaluating Treatment Response in RRMS

1. Begin DMT
2. MRI and clinical assessments at 6-12 months
   - Negative MRI result
     - Periodic clinical and MRI assessment
   - Active MRI result
     - Relapses and/or disease progression
       - Consider change of therapy
     - No relapses and no disease progression
       - Close clinical and MRI monitoring
MS Treatment - Injectables

- **Interferons**
  - BetaSeron (QOD,SQ)
  - Avonex (Weekly, IM)
  - Rebif (TIW, SQ)
  - Extavia (QOD,SQ)
- **Side Affects**
  - Flu like symptoms, Fatigue, Headache, Injection Problems

- **Treatment tricks**
  - Pre-medicate with Tylenol or Advil
  - Take medication before bed. Can disrupt sleep, so may need morning dosing
  - Determine hours until “worse” flu like symptoms and adjust shot to have them occur when sleeping

- **Labs**
  - LFTs Q6 months; TSH - yearly
MS Treatment - Injectable

- **Copaxone (CoPolymer)**
  - Believed to be equal to Interferons when used early (CIS)
  - Presently given daily - SQ
  - Probable change to every other day (double dose amount) in 2013

- **Side Affects**
  - Injection site reaction of itching at site
  - Chest Pain (rare)
MS Treatment - Infusion

- **Tysabri**
  - Used for failing 1st line
  - Aggressive 1st line
  - Progression while on 1st line
  - Connected to PML
    - 24 months use
    - Prior Chemotherapy
    - JC virus +
  - Can have steroids 2 weeks before infusions for flares
  - Continued reports of improving fatigue, cognitive and strength with starting
MS Treatment - Infusion

- **Tysabri**
  - **Labs/Imaging**
    - Check monthly labs, urine at time of infusion
    - Check JC Virus before starting and every 3 months after
      - Available through Quest Labs
    - Check MRI every 6 months JC(+) or yearly JC(-)
Requirements for PML Development:
JCV Mutation

Evidence from multiple patient populations supports the theory that specific JCV mutations contribute to the development of PML.

- **Wild-type / benign JCV**
  - Transmittable form
  - Commonly found in the kidney of healthy patients
  - May replicate periodically

- **Pathogenic JCV**
  - Active variant found in brains of PML patients
  - Contains mutations believed to increase viral replication and pathogenicity
  - Causes destruction of myelin-producing cells of the brain

Viral mutations
Evaluation of JCV DNA Testing

Quantitative PCR testing for JCV DNA

- 1,400 MS patients checked (13,000 samples)
  - Blood Tests
    - <1% and not associated with the development of PML
  - Urine samples
    - 25% Positive (Prior studies = 55%)

1 / 3 patients who developed PML were urinary JCV DNA negative at all time points tested

**Results suggested JCV DNA detection in blood or urine is not reliable for assessment of PML risk**
Indirect Testing

- Check Anti-JCV Antibodies (serum)
  - Initial exposure to the virus results in formation of anti-JCV antibodies

- Once seropositive, antibodies generally persist even during viral latency

- Currently the test is available through Quest Labs
# Anti-JCV Antibody vs. JCV DNA Testing

<table>
<thead>
<tr>
<th>Uses</th>
<th>STRATIFY JCV Test</th>
<th>JCV DNA Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Detects past JCV exposure</strong></td>
<td>• Detects past JCV exposure (does not diagnose PML)</td>
<td>• Diagnostic (CSF) for PML</td>
</tr>
<tr>
<td><strong>Can be used for assessment of PML risk</strong></td>
<td></td>
<td>• Denotes JCV actively replicating in the brain</td>
</tr>
<tr>
<td><strong>Diagnostic (CSF) for PML</strong></td>
<td></td>
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<td><strong>Denotes JCV actively replicating in the brain</strong></td>
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<table>
<thead>
<tr>
<th>Test type</th>
<th>• ELISA</th>
<th>• PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample</strong></td>
<td>• Blood</td>
<td>• Blood, urine, CSF</td>
</tr>
<tr>
<td><strong>Detects</strong></td>
<td>• Antibodies to JCV</td>
<td>• Presence of viral components (DNA)</td>
</tr>
<tr>
<td><strong>Results indicate:</strong></td>
<td>• Any past exposure to JCV</td>
<td>• JCV exposure, but only when JCV is actively replicating and shedding into test sample</td>
</tr>
</tbody>
</table>
Ongoing Research Evaluation

Among >800 MS patients tested:
- 46% were anti-JCV antibody negative
- 54% were anti-JCV antibody positive

A prospective clinical trial of >30,000 MS patients is ongoing to evaluate STRATIFY JCV to:
- Assess the prevalence of JCV in MS patients
- Determine changes in JCV antibody status over time
- Identify the correlation between JCV positivity and PML development
MS Oral Treatments

- Gilenya – Fingolimod
- Initially investigated to prevent renal allograft rejection
- Chemically modified derivative of a fungal metabolite
  - Studied against current Interferon (injectable) with:
    - 45% reduction in relapse rate compared to Interferon.
MS Oral Treatments

- **Gilena - Fingolimod**
  - **Mechanism of Action**
    - Agonist to S1P receptors
      - When Phosphorylated
    - Gilena acts to sequester circulating lymphocytes into secondary lymphoid organs
    - No effect on lymphocyte induction, proliferation, or memory function
    - Lymphocyte counts decreased by 72-77%
    - Peripheral reduction of
      - CD3+, CD4+, CD8+, - CD45RO+ (memory T cells),
      - CD45RA+ (naive T cells), - CD19+ cells
## Gilenya - Cardiac

<table>
<thead>
<tr>
<th>Number (%) of Participants</th>
<th>IFN β-1a 30µg IM Once Weekly</th>
<th>Oral Fingolimod 0.5mg</th>
<th>Oral Fingolimod 1.25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>2 (0.5%)</td>
<td>10 (2.4%)</td>
</tr>
<tr>
<td>Second Degree AV Block</td>
<td>0</td>
<td>1 (0.2%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>First Degree AV Block</td>
<td>0</td>
<td>1 (0.2%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicitis</td>
<td>2 (0.5%)</td>
<td>0</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Herpes viral infections</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>0</td>
<td>2 (0.5%)</td>
</tr>
</tbody>
</table>

* Cardiac Complications with First dose believed due to internalization of SP receptors
MS Oral Therapies
Gilenya (Fingolimod)

- FDA Requirements
  - A. 6 hour Observation with EKG with first dose and prior to leaving
    - Blood pressure every hour
  - B. OCT exam before and at 3-4 months
  - C. Varicella Titer

- MS Center of Lehigh Valley Gilenya Protocol
  - A. 6 hour Telemetry Monitoring
    *Dr. Spikol
  - B. OCT exam before and at 3-4 months
  - C. Varicella Titer
  - D. Cancer Screening
    - Dermatology
    - Male/Female Standard Guidelines
      - Breast, Pelvic, Testicular, Colon
MS Oral Therapies – Aubagio (Teriflunomide)

- Aubagio
  - FDA approved October 2012
  - Active component of Leflunomide

- Major Side Effects
  - Liver Affect
  - Alopecia
  - Birth Defects
Teriflunomide is the active metabolite of leflunomide
- Leflunomide is FDA-approved in adults for the treatment of active rheumatoid arthritis

Teriflunomide is being developed for the treatment of multiple sclerosis:
- Eliminates other metabolites of leflunomide
  - Although it is a minor pathway, these metabolites may themselves have adverse effects
- Avoids the hepatic metabolism of leflunomide to teriflunomide
- Reduces CYP450 involvement compared with leflunomide, which may decrease potentially clinically significant drug–drug interactions
Teriflunomide: Proposed MOA in MS

Teriflunomide selectively and reversibly inhibits DHODH

- a key mitochondrial enzyme in *de novo* pyrimidine synthesis required by rapidly dividing lymphocytes
  - Cystostatic
  - Limit over-activation of the activated and autoimmune Lymphocytes
  - Protective immunity is not significantly affected by Teriflunomide
MS Oral Therapies - Teriflunomide

- **Leflunomide Experience**
  - **Cases of Lymphoma have been seen**
    - However increase in case with all RA treatments (MethoTrexate, Cyclosporin)
  - **Severe Liver Necrosis with fatalities have occurred**
    - Seen within first 6 months of therapy
  - **Severe Infections have been seen**
    - TB, Pneumonia, PCP, Mycotic
Teriflunomide

- TEMSO (Teriflunomide Multiple Sclerosis Oral trial)
  - Decrease in Annual Relapse Rate (vs Placebo)
    - 7 mg dose – 31.2 %
    - 14 mg dose – 31.5 %

- TOWER
  - Decrease in Annual Relapse Rate (vs Placebo)
    - 7 mg – 22.3 %
    - 14 mg – 36.3 %
MS Oral Therapies - DMF

- DMF (dimethyl fumarate)
  - Derived from Fumaderm, an oral therapy of fumaric acid esters
  - Approved to treat psoriasis in Germany

- Initial Proposed FDA approval – December 2013

- Proposed for Mid 2013
  - FDA needed extended time to review Data.
  - Did not require more / additional data
DMF (DiMethyl Fumarate)

- Therapeutic mechanism in MS is speculative
  - Psoriasis Data -
    - Beneficial effect coincides with Lymphocytopenia
      » Decreased by 40%-60%
    - Down-regulation of proinflammatory cytokines
    - Increase in Antiinflammatory cytokine IL-10
    - Upregulation of Nuclear Factor 2
    - Induces Anti-Inflammatory Stress Protein HO-1

- Protective antioxidant pathway in CNS
  - Unpublished data in the EAE model
MS Oral Therapies - DMF

■ DEFINE:
  - Placebo-controlled, 1011 patients
    - Low-dose: 240 mg BID
    - High-dose: 240 mg TID
    - Annualized relapse rate
  - Results
    - Two year ARR –
      - Placebo = 36%, BID = 17%, TID = 19%

■ CONFIRM:
  - High- and low-dose vs Copaxone®
  - Subjects (N~1232): RRMS by MacDonald, EDSS <5
  - Primary outcome: Annualized relapse rate
  - Results
    - Two year ARR –
      - Copaxone = 29%, BID = 22%, TID = 20%
Conclusion

- MRI is now major diagnostic tool
  - Can diagnose with first attack / MRI
  - Clinically Isolated Syndrome and Radiological Isolated Syndrome categories

- New Oral Therapies