Multiple sclerosis: Clinical Viewpoint: Examples of analytical issues in neurological diseases

In: Symposium on Statistical Issues in the Analysis of Neurological Studies
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Tanuja Chitnis MD
MULTIPLE SCLEROSIS

- Demyelinating and degenerative disease of the central nervous system predominantly involving white matter

- Hallmark: lesions in time and space

Trapp et al, NEJM;338:278-85 1998
EPIDEMIOLOGY

- Affects 60-100/100,000 persons
- 0.1% of population = 400,000 in US

- Median age onset 23.5 years
- Mean age onset 30 years
- 1.77:1.00 female: male ratio
- 5 years earlier in females than males

- Mean age of death 58.1 years (vs. 70.5)
- Sibling risk 3-5%
- Monozygotic twins exhibit 25% concordance rate
Disease course

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Relapsing</th>
<th>Progressive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disability</strong></td>
<td><img src="image" alt="Graph showing disability progression" /></td>
<td><img src="image" alt="Graph showing disability progression" /></td>
</tr>
<tr>
<td><strong>Lesion Burden</strong></td>
<td><img src="image" alt="Graph showing lesion burden progression" /></td>
<td><img src="image" alt="Graph showing lesion burden progression" /></td>
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<tr>
<td><strong>Atrophy</strong></td>
<td><img src="image" alt="Graph showing atrophy progression" /></td>
<td><img src="image" alt="Graph showing atrophy progression" /></td>
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<tr>
<td><strong>Gd-lesions</strong></td>
<td><img src="image" alt="Graph showing Gd-lesions progression" /></td>
<td><img src="image" alt="Graph showing Gd-lesions progression" /></td>
</tr>
</tbody>
</table>

RELAPSE SYMPTOMS IN MS

• Typical presenting symptoms of relapses:
  • Optic neuritis
  • Sensory (26%)
  • cranial nerve/brainstem
  • Gait disorder

• Cognitive dysfunction
• Depression
• Fatigue
Disability accumulation

EDSS: Expanded Disability Status Scale

- EDSS 0.0
- EDSS 1.0
- EDSS 2.0
- EDSS 3.0
- EDSS 4.0
- EDSS 5.0
- EDSS 6.0
- EDSS 7.0
- EDSS 8.0
- EDSS 9.0

Progression of disability levels shown with icons and cane illustrations.
HETEROGENEITY DISEASE COURSE

• Disability measured using the EDSS (Expanded Disability Status Scale) 0-10

• Benign MS - EDSS of less than 2 within 15 years of onset (≈15%)

• Malignant MS - EDSS of 6 within 5 years (≈15%)
T2 MRI lesions – reflect areas of inflammation
Brain volume as a measure in MS

• Brain morphometry: brain parenchymal fraction (BPF) measured by TDS+ pipeline: $BPF = \frac{WM + GM}{WM + GM + CSF} = 1 - \frac{CSF}{ICC}$
Possible Mechanisms of Injury and Repair in Multiple Sclerosis.

90% of MS (9/10) therapies target peripheral blood mechanisms.
# DIFFERENT MECHANISMS OF RELAPSING AND PROGRESSIVE MS

<table>
<thead>
<tr>
<th>RELAPSING MS MECHANISMS</th>
<th>PROGRESSIVE MS MECHANISMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• T Cell activation</td>
<td>• Cortical lesions and gray matter pathology</td>
</tr>
<tr>
<td>• APC activation</td>
<td>• Dying back axonopathy</td>
</tr>
<tr>
<td>• Epitope spreading</td>
<td>• Diffuse activation of glial cells – microglia and astrocytes</td>
</tr>
<tr>
<td>• B cell stimulation</td>
<td>• Mitochondrial dysfunction and oxidative stress</td>
</tr>
<tr>
<td>• Antibody production</td>
<td>• Presence of meningeal follicles</td>
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<tr>
<td></td>
<td>• Impaired CNS repair processes</td>
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</table>
Unanswered questions in MS:

1. Risk factors including genetic predictors of MS disease versus health
2. Predictors of conversion from a monophasic form of MS to chronic disease
3. Predictors and correlates of disability accumulation in MS
4. Predictors of response to specific MS treatments
Outcomes in MS:

1. Questions 1 and 2:
   • MS versus health

2. Questions 3 and 4:
   1. Number of relapses (annualized)
   2. Disability score (EDSS score)
   3. MRI measures (T2 lesion volume, brain atrophy, many others...)  
   4. Patient reported outcomes – quality of life, real-world measures
   5. Health economics (ER visits, cost etc)

6. Outcome depends on who you are, and your question of interest
   • (patient, doctor, payor)
Outcomes in MS: Challenges

1. Accuracy of measures – intra-rater and inter-rater variability
2. Reproducibility between studies/cohorts
3. Longitudinal “drift” in protocols, measures
4. Change in measures/machines – example: MRI 1.5T to 3T change
5. Correlation between outcomes?
6. Do the outcomes really measure what is important (example – sustained progression)
Predictors in MS

1. Genetics
2. Environmental exposures
3. Preceding medical issues
4. Preceding disease course
5. Biomarkers – blood, MRI
Predictors in MS: Challenges

1. Do we have all the right predictors? – Data gathering war

2. Relevance of predictor gathered – (example: on treatment blood biomarker)

3. Frequency and effect of predictor

4. Dependency of predictors
Analysis in MS: Challenges

1. Univariate versus multivariate analysis:
   • List of features is growing.....

2. Accounting for treatment in analyses

3. Separating “natural history” of disease from “treatment effect”
**CLIMB Medical Director**
Tanuja Chitnis, MD
Director, Partners MS Center
Howard Weiner, MD

**Director, Clinical Research Operations**
Bonnie Glanz, PhD
Head of Biostatistics
Brian Healy, PhD

**CLIMB Study Staff**
Sandra Cook, RN
Mira Weiner
Study Coordinators
Grace Little
Emily Greeke

**Immunology/Biomarkers**
Roopali Gandhi, PhD
Pia Kivisäkk, MD PhD
Francisco Quintana, PhD
Philip De Jager, MD PhD
IT/Database
Database Manager
Software Architect
System Administrator
Data Analyst
Mariann Polgar-Turcsanyi, MS
Adam Polgar
Mark Anderson
Alicia Chua, MS

**Neuroimaging Research**
Rohit Bakshi, MD
Charles Guttmann, MD
MRI Analyst
Svetlana Egorova, MD PhD

**Goal:** To follow 2000 MS patients for 20 years using detailed clinical, MRI and biological studies
- bi-annual neurological assessments
- annual MRI brain (spine every 2 years)
- annual QOL, brief cognitive battery
- annual blood draw - PBMC and serum evaluation
- genetic testing
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**Overview of CLIMB Study Data Collection including number of datapoints (listed within boxes) collected at each visit:**

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### Decision Point: 6 Months Since Last Visit

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<th>Visit 1</th>
<th>Visit 2</th>
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<tr>
<td><strong>T2 Lesions [number]</strong></td>
<td>9</td>
<td>15</td>
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</tbody>
</table>

#### Make Change?
- **No**
- **Yes**

- Medication 1
- Medication 2
- Medication 3
- Medication 4
- Medication 5
CLIMB Study Investigators