Risk Factors for Disability Progression in Multiple Sclerosis

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Risk Factors for Disability Progression in Multiple Sclerosis

- Disability progression in MS is a major clinical concern
- Evidence by the fact that the therapeutic target of DMT is to delay/prevent disability progression
- Having a better understanding of factors that increase the risk of disability progression will:
  - Aid clinicians in treatment choices
  - And assist in counseling patients about prognosis
Risk Factors for Disability Progression in Multiple Sclerosis

- The impact of comorbidities on disability progression in MS
  - Overview of the increasing prevalence & incidence of MS
  - Review of literature and our findings on comorbidities as a risk factor for disability progression

- Dr. Wallin will follow
  - Presents data on the influence of age, gender and race on disability progression
The Impact of Comorbidities on Disability Progression in MS

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Disclosures - Support

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Learning Objectives

- Provide an overview of the changing epidemiology of MS
- Present results of analyses of risk factors for disability progression from a modern MS incident cohort
- Discuss our findings with that from recent literature in an attempt to draw some general conclusions on risk factors for disability progression
Changing MS Epidemiology

- Numerous studies have shown that the incidence and prevalence of MS has increased over the past couple of decades.
- Rates are raising faster in females with recent studies showing nearly a 4:1 ratio to males.
- MS is now occurring at moderate to high rates in populations historically believed to be at low risk for MS.
- Rates among African Americans have been demonstrated to be higher than in Caucasians.
Changing MS Epidemiology

- Conducted meta-regression analysis of studies on MS prevalence and incidence in Europe and North America (178 studies meeting inclusion criteria)
- Used weighted linear regression to assess the effects of latitude, time and gender on MS prevalence and incidence
Figure 4: Prevalence and incidence in western Europe and North America by year
Estimates and 95% CI are shown. (A) The correlation of prevalence with time, although significant, was weak ($r^2=0.11; p<0.001$. Correlation between prevalence and time was more pronounced when analysed for high and low northern latitudes separately (below 52°N $r^2=0.12; p=0.006$; at or above 52°N $r^2=0.28; p<0.001$. (B) The correlation between incidence and year for western Europe and North America was significant ($r^2=0.16; p<0.001$).

Figure 6: Sex ratio (female: male) by latitude, year, and incidence rates
Log-transformed sex ratios (95% CI) were used for regression analyses. (A) Sex ratio decreased with latitude: corresponding to a factor 0.99 decrease per degree northern latitude (p=0.006). In cases of repeated surveys, only the most recent value was used. (B) Sex ratio increased with year: corresponding to a factor 1.014 increase in sex ratio per year (p<0.001). (C) Sex ratio was also weakly associated with incidence rate: corresponding to a factor 1.05 increase in sex ratio per unit incidence increase (p<0.001). Dotted lines indicate lines of regression.

Changing MS Epidemiology

- Assessed prevalence and change in age-distribution over time in Manitoba
- Cases identified from claims database
  - 1984 to 2006
  - Positive predictive value = 80.5%
  - National data captures ≈ 96% of the population
- Prevalence & incidence age-standardized to the 2005 province census data
Figure 1. Age-standardized incidence of MS in Manitoba per 100,000 population from 1998 to 2006.

Figure 2. Age-standardized prevalence of MS in Manitoba per 100,000 population from 1984 to 2006.

**Figure 2.** Age-specific prevalence of MS in Manitoba per 100,000 population by year between 1984 and 2004.

Changing MS Epidemiology

- Recent studies in areas considered to be generally at low risk for MS are now reporting moderate to high prevalence.

- For example:
  - **Greece**: 119 / 100,000 [Papathanasopoulos et al. Neuroepidemiology 2008; 30: 167-73]
  - **Qatar**: 93 / 100,000 [Deleu et al. MSJ 2013; 19(6): 816-19]
  - **Kuwait**: 85 / 100,000 [Alroughani et al. MSJ 2014; 20(5): 543-47]
  - **Cyprus**: 55 / 100,000 [Dean et al. J Neurol Sci 1997; 145: 163-68]
  - **Turkey**: 51 / 100,000 [Turk-Boru et al. Neuroepidemiology 2011; 37: 231-35]
  - **Iran**: 51 / 100,000 [Elhami et al. Neuroepidemiology 2011; 36: 141-47]
Changing MS Epidemiology: Military Cohorts

- Incidence of MS in active duty military found a 10-year IR of 12.9 per 100,000 person-years (Deussing et al. Milt Med 177; 5: 594-600)
  - Black non-Hispanic: IR of 18.3 / 100,000 PY
  - White non-Hispanic: IR of 12.5 / 100,000 PY
- One of first studies to show higher incidence among African Americans compared to Caucasians
Changing MS Epidemiology: Military Cohorts

- Gulf War Era MS Cohort (1999-2007)

- Average annual incidence
  - Total: 9.6 per 100,000 [9.26 – 9.99]
  - Males: 7.3 [6.98 – 7.67]
  - Females: 24.7 [23.10 – 26.36]
  - Caucasian: 9.32 [8.90 – 9.76]
  - RR_F:M was 3.39 [3.13 – 3.67]
  - RR_AA:C was 1.27 [1.16 – 1.39]
Changing MS Epidemiology

- The existing data suggest a rather robust increase in the prevalence and incidence of MS worldwide.
- Some studies suggest that incidence may be plateauing while others suggest the incidence is still increasing.
- There is greater concordance that the prevalence of MS has, and continues to increase.
- The increase in the incidence/prevalence of MS appears to be accounted for:
  - Predominantly by an increase in women.
  - Secondarily by an increase among African Americans.
Changing MS Epidemiology

- The increased incidence/prevalence appears to be due to
  - Better and earlier ascertainment
  - Better treatment resulting in longer survival
- The MS population is ageing as prevalence increases
- It is well recognized that comorbidities increase with age and adversely impact
  - Management of chronic diseases
  - Overall health status
  - Quality of life
Comorbidity and MS

- Comorbidity (CMB) refers to the adverse impact of conditions/diseases/disorders other than that due to the primary condition/disease/disorder.
- CMB in chronic diseases such as MS are often under-appreciated, although this is changing.
- There is a growing literature on CMB in MS.
- The next section provides a brief review of the effects of CMB on disability progression.
Comorbidity and MS: Measurement

- **Data source(s)**
  - Chart review
  - Patient reported (survey or during HC encounter)
  - Administrative/claims databases

- **Measurement scale**
  - Indicators for specific CMBs
  - Summary score of comorbidity status (e.g. Charlson)

- **Choice depends on**
  - Availability of data sources
  - Intended use of the CMB measure
Comorbidity and MS

- CMB has been found to negatively impact patients with MS as early as the time of diagnosis

- Analysis of NARCOMS data from 2006
  - $N = 8,983$ respondents
  - Self-reported CMB and disability (PDDS)
  - Assessed impact of CMB on
    - Diagnostic delay
    - Disability
Comorbidity and MS

- CMB was associated with diagnostic delay that was more pronounced the younger the patient.
- After adjusting for year of symptom onset and gender:
  - <25 yo: Dx delay ≈ 7.52 yrs.
  - ≥25 & <40 yo: delay ≈ 3.15 yrs.
  - ≥40 yo: delay ≈ 1.3 yrs.
**Comorbidity and MS**

<table>
<thead>
<tr>
<th>Comorbidity category</th>
<th>Moderate vs mild</th>
<th>Severe vs mild</th>
<th>Adjusted for diagnostic delay*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
</tr>
<tr>
<td>Vascular</td>
<td>1.51</td>
<td>1.12-2.05</td>
<td>1.06</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1.54</td>
<td>1.04-2.28</td>
<td>1.81</td>
</tr>
<tr>
<td>Mental</td>
<td>1.29</td>
<td>0.97-1.71</td>
<td>1.62</td>
</tr>
<tr>
<td>Overweight*</td>
<td>1.08</td>
<td>0.78-1.50</td>
<td>1.03</td>
</tr>
<tr>
<td>Obesity*</td>
<td>1.38</td>
<td>1.02-1.87</td>
<td>1.24</td>
</tr>
</tbody>
</table>

Vascular: diabetes, hypertension, heart disease, peripheral vascular disease, hypercholesterolemia; Musculoskeletal: fibromyalgia, arthritis, rheumatoid arthritis, systemic lupus erythematosus, hip replacement, knee replacement; Mental: depression, anxiety, bipolar disorder, schizophrenia; Overweight: body mass index (BMI) 25 kg/m² and 30 kg/m²; Obesity: BMI 30 kg/m². Autoimmune, gastrointestinal, and visual comorbidities were not associated with disability at diagnosis.

*All models adjusted for sex, age at symptom onset, year of symptom onset, and income.
†Included in the same Cox model as indicator variables with normal weight as the reference group.

NARCOMS: North American Research Committee on Multiple Sclerosis; OR: odds ratio.

Comorbidity and MS

- Assessment of vascular CMB on disability progression
- Vascular CMB included: diabetes, hypertension, heart disease, peripheral vascular disease, hypercholesterolemia
- Cox Proportional Hazard adjusting for sex, year of onset, income, race
  - Presence of 1+ vascular CMB had a HR of 1.51 [1.41 – 1.61] for early gait disability
  - Vascular CMB any time during disease course had HR of 1.54 [1.44 – 1.65]
  - Median time from diagnosis to ambulatory aid was 18.8 years in patients without vascular CMB compared to 12.8 years in those with vascular CMB
Comorbidity and MS

- Assessment of cardiac CMB: frequency and economic impact
  - Focused on cardiac conditions that would preclude use of Fingolimod
  - 2006 – 2010 National Inpatient Sample (NIS)

- Results
  - Among 136,542 discharges 9.2% had a cardiac condition that would preclude use of Fingolimod
  - Patients with cardiac conditions were significantly older and had nearly twice the total number chronic conditions
Comorbidity and MS

- Depression is a common comorbidity in MS patients
  - Prevalence of depression is nearly twice that in the general population (15.7% vs. 7.4%)
  - As many as 50% of MS patients experience depressive symptoms that may not always result in a clinical diagnosis but yet have clinical consequences

- Treatment with INFβ is associated with depression
  - 41% (35 of 85) MS patients on INFβ-1b reported new or worsening depression within 6 mos of beginning therapy
Comorbidity and MS

- Adherence with DMT adversely impacted
  - 11 of the 35 patients reporting depression discontinued DMT
  - Depression was significantly associated with discontinuation

- Treatment of depression improved adherence
  - Treatment consisted of
    - Antidepressants 9 (26%)
    - Psychotherapy 5 (14%)
    - Antidepressants and psychotherapy 13 (37%)
  - Patients not treated for depression were significantly more likely to discontinue DMT

- Assuring adherence is critical to minimize the disability progression
Comorbidity and MS: The VHA Experience

■ Analysis of survey data from the MSSR
  ▪ Multiple Linear Regression
  ▪ Outcome
    • Patient Determined Disease Steps
  ▪ Predictor
    • DMT-R
  ▪ Control Variables
    • Age, gender, race, number of comorbidities
    • DX before 1994, disease duration, smoking
## Comorbidity and MS: The VHA Experience

<table>
<thead>
<tr>
<th>Variable</th>
<th>B ( SE)</th>
<th>95 % CI (LB, UB)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMT-R = 0.0</td>
<td>.094 .21</td>
<td>-.323, .511</td>
<td>.442</td>
<td>.659</td>
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<tr>
<td>DMT-R = .0001 to .2734</td>
<td>.570 .23</td>
<td>.116, 1.024</td>
<td>2.463</td>
<td>.014</td>
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<tr>
<td>DMT-R = .2735 to .5333</td>
<td>.485 .21</td>
<td>.067, .902</td>
<td>2.278</td>
<td>.023</td>
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<tr>
<td>DMT-R = .5334 to .8750</td>
<td>.346 .20</td>
<td>-.039, .731</td>
<td>1.762</td>
<td>.078</td>
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<td>YR DX (1= before 1994)</td>
<td>.402 .16</td>
<td>.091, .713</td>
<td>2.535</td>
<td>.011</td>
</tr>
<tr>
<td>Current Age (yrs)</td>
<td>.138 .06</td>
<td>.025, .251</td>
<td>2.401</td>
<td>.017</td>
</tr>
<tr>
<td>Age$^2$</td>
<td>-.001 .01</td>
<td>-.002, .000</td>
<td>-2.016</td>
<td>.044</td>
</tr>
<tr>
<td>Gender (1=male)</td>
<td>.492 .14</td>
<td>.222, .763</td>
<td>3.570</td>
<td>.000</td>
</tr>
<tr>
<td>Comorbidities (total #)</td>
<td>.220 .03</td>
<td>.154, .287</td>
<td>6.502</td>
<td>.000</td>
</tr>
</tbody>
</table>

Intercept = -0.37  1.49 (95%CI : -3.29, 2.56), p = .81
SUMMARY

- There is compelling evidence that the incidence and prevalence of MS is increasing with penetrance into areas historically believed to be at low risk.
- As MS prevalence has increased so has the age of the MS population.
- Comorbid (CMB) conditions increase with age that can complicate treatment and exacerbate disease severity.
- Several studies have shown a direct impact of CMB as early as the time of diagnosis in:
  - Diagnostic delay
  - Time to PDDS 6 (requires ambulatory aid)
An unresolved question is what is the best method for measuring CMB in the MS, or any chronic disease, patient population.

Several studies out of Manitoba (Marrie RA) have published case definitions for a variety of individual CMBs using claims data.

Summary measures such as the Charlson & Elixhauser were designed and validated on inpatient populations and track a limited number of CMB conditions.
SUMMARY

- We have been funded by the NMSS (Culpepper: PI) to develop a CMB measure specifically for use in the MS population (CMBms)
- Stay tuned... by this time next year we should have data to share on our progress with the development of the CMBms
- Evaluation of CMB should be evaluated annually at a minimum
- Appropriate referral and management of CMB imperative to
  - Minimize the direct impact(s) on disability progression
  - Reduce the risk of non-adherence and discontinuation of DMT
Epidemiology & Outcomes Team

- Joel Culpepper, PhD, MA
- Mitch Wallin, MD, MPH
- Shan Jin, PhD
- Heidi Maloni, RN, PhD
- Jill Settle, MA
- Walter Royal, MD
- Chris Bever, MD
Obtaining CME/CE Credit

- If you would like to receive continuing education credit for this activity, please visit:

- QUESTIONS
DMT-R

- DMT use ratio (DMT-R)
  - DMT treated as a “class” like in Brown (2007)

<table>
<thead>
<tr>
<th>DMT-R</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>215 (21.5%)</td>
</tr>
<tr>
<td>.0001 - .2734</td>
<td>155 (15.5%)</td>
</tr>
<tr>
<td>.2735 - .5333</td>
<td>197 (19.7%)</td>
</tr>
<tr>
<td>.5334 - .8750</td>
<td>224 (22.4%)</td>
</tr>
<tr>
<td>.8751 – 1.000</td>
<td>208 (20.8%)</td>
</tr>
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</table>