Multiple Sclerosis:
Risk Factors for Onset
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Disclosures
No conflicts of interest to declare
Topical Outline

- Environmental Risk Factors for MS Onset
  - Geography
  - Infectious triggers
  - Smoking
  - Obesity
  - Vitamin D
- Military Deployment and MS

Evidence for Environmental Susceptibility in MS

- Geographic Risk Gradients
- Migration & MS risk
  - Low Prevalence zone → High Prevalence Zone
  - High Prevalence zone → Low Prevalence Zone
  - Israel
- Epidemics of MS
- Viral models
Familial Aggregation and MS Risk

Population-based prevalence (per 1,000)

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td></td>
</tr>
<tr>
<td>Adoptive siblings</td>
<td></td>
</tr>
<tr>
<td>First cousin</td>
<td></td>
</tr>
<tr>
<td>Paternal half sibling</td>
<td></td>
</tr>
<tr>
<td>Maternal half sibling</td>
<td></td>
</tr>
<tr>
<td>Full sibling</td>
<td></td>
</tr>
<tr>
<td>HLA Identical sibling</td>
<td></td>
</tr>
<tr>
<td>Monozygotic twin</td>
<td></td>
</tr>
<tr>
<td>Offspring Conjugal Pair</td>
<td></td>
</tr>
</tbody>
</table>

Candidate Genes in MS
(adapted from Baranzini S, *Curr Opin Neurol* 2012)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA DRB1</td>
<td>6</td>
<td>2.3-6.4</td>
</tr>
<tr>
<td>IL2RA, interleukin 2 receptor</td>
<td>10</td>
<td>1.25</td>
</tr>
<tr>
<td>IL7R, interleukin 7 receptor</td>
<td>5</td>
<td>1.18</td>
</tr>
<tr>
<td>CLEC16A, C-type lectin domain family 16, A</td>
<td>16</td>
<td>1.14</td>
</tr>
<tr>
<td>RPLS, ribosomal protein LS</td>
<td>1</td>
<td>1.15</td>
</tr>
<tr>
<td>DBC1, deleted in bladder cancer 1</td>
<td>9</td>
<td>1.17</td>
</tr>
<tr>
<td>CD58, lymphocyte function-associated antigen 3</td>
<td>1</td>
<td>1.24</td>
</tr>
<tr>
<td>ALK, anaplastic lymphoma receptor tyrosine kinase</td>
<td>2</td>
<td>1.37</td>
</tr>
<tr>
<td>FAM69A, family with sequence similarity 69, A</td>
<td>1</td>
<td>1.12</td>
</tr>
<tr>
<td>SCO2, cytochrome c oxidase assembly protein</td>
<td>22</td>
<td>1.09</td>
</tr>
</tbody>
</table>
Genetic Susceptibility and MS

- Genome wide association studies in MS have established over 100 common variants
- Genome wide variants contribute little in explaining overall MS risk
- Environmental and epigenetic modifications on genome require further study
- Susceptibility genes “load the gun”

Geography
MS Prevalence & Incidence Trends
(Koch-Henriksen, Lancet 2010)

Incidence vs Latitude
Incidence vs Time

MS in US Veterans during 20th Century
Infectious Triggers

Environmental Risk and MS
Two Theories of Infectious Causation

- Both espouse MS is a rare complication of a widespread infection
  - “Prevalence hypothesis” (J. Kurtzke): MS is caused by an infection more common in geographic regions of high risk
  - “Hygiene hypothesis” (E. Acheson): MS is caused by a late age acquisition of an infection commonly acquired in early childhood
Epstein Barr Virus and MS Risk
(Thacker E, Ann Neurol 2006)

Relative Risk of MS for the highest compared with the lowest tertile of Abs in serum collected > 5 years before symptom onset (N=73 MS cases, 219 cts)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Bivariate Analysis RR (95% CI)</th>
<th>Multivariate Analysis RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV-EBNA-1</td>
<td>4.2 (1.9-9.2)*</td>
<td>4.5 (1.9-11)*</td>
</tr>
<tr>
<td>EBV-VCA</td>
<td>1.1 (0.57-2.3)</td>
<td>0.86 (0.38-2.0)</td>
</tr>
<tr>
<td>HSV</td>
<td>0.63 (0.32-1.2)</td>
<td>0.59 (0.25-1.4)</td>
</tr>
<tr>
<td>VZV</td>
<td>1.1 (0.60-2.2)</td>
<td>0.94 (0.44-2.0)</td>
</tr>
<tr>
<td>Measles</td>
<td>2.4 (1.1-5.6)*</td>
<td>1.4 (0.52-3.6)</td>
</tr>
<tr>
<td>HHV-6</td>
<td>2.4 (1.2-4.8)*</td>
<td>2.3 (1.0-5.1)*</td>
</tr>
</tbody>
</table>

Human herpes viruses and MS (Sundström P, Neurology 2004)

Relative Risk of MS for the highest compared with the lowest tertile of Abs in serum collected > 5 years before symptom onset (N=73 MS cases, 219 cts)
EBV Antibody titers and MS Onset
(Levin L, JAMA 2005)

- Nested case-control study utilizing DoD Serum Repository (N=83 cases)
- Pre-illness serum collected on average 4 years prior to MS onset sx
- Serum EB Nuclear Antigen increased 2- to 3-fold after age 20 in MS cases
- RR of MS 3.0 (95% CI: 1.3-6.5) with a 4-fold increase in anti-EBNA Abs

Geometric mean titers of EBNA IgG by age

HLA and EBV in risk of MS
(De Jager P, Neurology 2008)

- Nested case-control study NHS/NHS II (N=148 women, 18 with pre-onset serum)
- Anti-EBNA-1 RR for MS did not change after statistically adjusting for DR15 allele status
- 9-fold increase in RR for MS between EBNA-1 Ab titers > 1:320/HLA DR15+ and cases with low EBNA-1 Ab titers/HLA DR15-
EBV as a candidate virus in the etiology of MS

- Epidemiology: supportive, increased risk of MS with late infection
  - Low overall # of late EBV infections
  - Doesn’t explain Faroe Islands Epidemic
  - Doesn’t explain low ➔ high risk migration
- EBV sero-reactivation associated with relapses (Wandinger K, Neurology 2000)
- EBV found within B-cell follicles in CNS (Serafini B, J Exp Med, 2007), but not reproduced by another group (Willis S, Brain, 2009)
- Increasing titers of EBNA-1 antibodies in MS cases likely related to another infection

Smoking & Risk for MS Onset
Smoking and risk for MS onset

- Search for studies between 1960-2010 (n=1490)
- 10 studies suitable for inclusion in a conservative model
- Overall RR=1.48 (95% CI: 1.35-1.63)
- Effect sizes uniformly distributed around the meta-analysis effect size indicating no major publication bias

Smoking & MS Onset Risk
(Hedstrom, *Eur J Epidemiol* 2013 & *Neurology* 2009)

Swedish population-based case-control studies
- Clear dose-response relationship between smoking and MS onset
- Detrimental effects abate after 10 years of smoking cessation
- No clear relationship between age of onset and risk for MS
- Use of Swedish snuff tobacco not associated with increased MS risk
Effects of Smoking & HLA Genes on MS Risk  
(Hedstrom, et al. *Brain* 2011 and *Int. J. Epid* 2014)

- The risk of developing MS associated with different HLA genotypes is influenced by both active and passive smoking
- Active smokers: Compared with non-smokers with neither of the genetic risk factors, the odds ratio was 13.5 (8.1–22.6) for smokers with both genetic risk factors
- Passive smokers: Non-exposed subjects with the two risk HLA genotypes had an OR of 4.5 (95% CI 3.3–6.1) vs. same genotype for subjects exposed to passive smoking rendered an OR of 7.7 (95% CI 5.5–10.8)
- Priming the immune system in the lungs may lead to MS in those with genetic susceptibility

Obesity and MS Risk
Obesity & MS Risk for Onset

- For women in the Nurses Health Study, obesity at age 18 years was associated with a 2.25 adjusted RR (95% CI: 1.50-3.37) for MS onset. (Munger, *Neurology* 2009)

- A Swedish population-based case-control study found a two-fold significant risk for MS in men and women with BMI > 27 kg/m² at age 20 years (Hedstrom, *Mult Scler* 2012)

- In a pediatric MS cohort in Kaiser Southern California, obesity was associated with an increased odds of developing CIS/MS in girls (Langer-Gould A, *Neurology* 2013):
  - Overweight vs. normal weight: OR: 1.58 (95% CI: 0.71-3.50)
  - Moderately obese: OR 1.78 (95% CI: 0.70-4.49)
  - Moderately obese vs. normal weight: OR 3.76 (95% CI: 1.54-9.16)

Obesity & Mechanisms for Immune Activation (Versini, 2014)

1) Adipokines produce pro-inflammatory state & deregulate Th17/Treg balance

2) Increase Apoptosis Inhibitory Macrophages (AIM) in blood

3) Promotion of Th17 profile

4) High fat diet may impact gut microbiome and deregulate Th17/Treg balance

5) “Lower” Vitamin D levels
Interaction among adolescent obesity, carriage of HLA-DRB1*15 (Hedstrom, *Neurology* 2014)

- In the EIMS incident cohort, obese subjects with the most susceptible genotype (DRB1*15 & absence of A*02) had an OR of 16.2 (95% CI 7.5–35.2) vs. nonobese subjects without the genetic risk factors.
- Corresponding OR in the KPNC prevalent study was 13.8 (95% CI 4.1–46.8).
- Significant interaction was observed between HLA-DRB1*15 and obesity, regardless of HLA-A*02 status.
- Prevention of adolescent obesity may lower the risk of developing MS.

Vitamin D and MS Risk
Vitamin D Metabolism & Effects

- Fat-soluble vitamin that has 2 major forms D2 (ergocalciferol) & D3 (calciferol)
- Most vitamin D produced via UV light in epidermis. 25-OH Vitamin D is best indicator of human vitamin D status
- Effects on CNS:
  - Neurotrophic support on NGF
  - Mediate neurotransmitters
  - Neuroprotection in glutamate-induced cell death of cortical neurons in animal models

Vitamin D & MS Risk

- Two to three sera samples from the DoDSR were seasonally adjusted and stratified by quintile of 25-OH vitamin D and the odds of developing MS was assessed
- Those in the highest quintile of 25-OH vitamin D among non-Hispanic whites had a significantly attenuated risk for MS (Odds ratio (OR) 0.38, 95% Confidence Interval (CI) 0.19-0.75).
- No significant risk for MS was shown for any quintile of 25-OH vitamin D for blacks or the other race group that included Hispanics and Asians.

Munger K, *JAMA* 2006
Vitamin D and MS Onset

- Optimal dose and normal range of Vitamin D not clear (IOM, 2011)
- Differences in polymorphisms in vitamin D-binding protein gene and bio-available Vitamin D between racial groups (Powe, 2013)
- Reverse causation between Vitamin D and MS not ruled out
- Goal of 40 nmol/L 25-OH for adults is reasonable

Military Deployment and MS Risk
Potential Risk Factors for MS in Gulf War-era Veterans

- **Vaccinations**
  - Anthrax (Kerrison, 2002)
  - Hepatitis B (Hernán, 2004)

- **Viral infections**
  - Parvovirus B19 aplastic crisis 1991 in Gulf region (Mallouh, 1995)

- **CNS toxins**
  - Sarin
  - Pyridostigmine bromide
  - Organic solvents (Riise, 2002)

- **Air pollutants (Oikonen, 2003)**

ALS and Gulf War Veterans (Neurology, September 2003)

- Horner, et al used active & passive surveillance to determine incidence rate of ALS 1990-2000
- 107 cases among 2.5 million veterans; incidence 0.43 per 100,000 persons/yr
- RR ALS 1.9 in GW Vets compared with nondeployed controls
- Haley, et al showed a higher incidence rate in deployed GW Veterans < 45 yrs
Neurologic Mortality in GW Veterans (Barth S, Am J Indus Med 2009)

- 13-year mortality follow-up in GW Veterans (N=621,902) vs. non-deployed veterans (N=746,248)
- Adjusted Mortality Rate Ratios:
  - Primary brain cancer: 0.61 (95% CI: 0.56-1.62)
  - Parkinson’s disease: 0.71 (95% CI: 0.17-2.99)
  - ALS: 0.96 (95% CI: 0.56-1.62)
  - MS: 0.61 (95% CI: 0.23-1.63)
- Environmental Exposure (sarin and oil well fire):
  - Primary brain cancer aRR=2.71 (95% CI: 1.25-5.87)

GW1 Deployment & MS Risk (Wallin, et al. Neuroepidemiology 2014)

- GW era MS cohort used to answer question of MS risk after deployment to GW1
- Entire GW1 population utilized in analysis:
  - 387 MS cases/696,118 deployed to GW1
  - 1,454 MS cases/1,796,215 not deployed
- Overall relative risk: 0.69 (CI: 0.61-0.78)
  - All service branch and sex specific RR < 1.0
  - Exposure to sarin was not a risk factor for MS onset
MS Risk Factors for Onset

Conclusions

- Geography, EBNA-1 Abs, smoking & obesity are significant risk factors for MS onset
- Vitamin D and MS risk for onset significant association for whites
- Deployment to GW1 is not a risk factor for MS
- Education and prevention approaches for modifiable MS risk factors in high risk groups
- Environmental risk factors require validation in larger, ethnically diverse cohorts
  - Interaction between risk factors
  - Gene-environmental interaction