Incidence & Clinical Features of Multiple Sclerosis

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Mitchell T. Wallin, MD, MPH
Clinical Associate Director
VA MS Center of Excellence East-Baltimore

Associate Professor of Neurology
Georgetown University School of Medicine
University of Maryland School of Medicine
Disclosures

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Learning Objectives:

- Recognize the importance of military cohorts in understanding the epidemiology of multiple sclerosis
- Discuss current findings regarding the incidence of multiple sclerosis
- Describe the current clinical features of MS in a diverse demographic population-based sample
Topical Outline

- MS and Epidemiology
- Environmental Risk Factors for MS Onset
  - Geography
  - Infectious triggers
- Military Deployment and DoD-VA Cohort Studies
Original Officers
AAN Section of Neuroepidemiology (1967-1971)

L. Kurland (Chairman)  
J. Kurtzke (Vice-Chairman)  
M. Alter (Secretary)
Evidence for Environmental Susceptibility in MS

- Geographic Risk Gradients
- Migration alters MS risk
  - Low Prevalence zone → High Prevalence Zone
  - High Prevalence zone → Low Prevalence Zone
  - Israel
- Epidemics of MS
  - Faroe Islands
MS Disease Timeline
Familial Aggregation and MS Risk
(adapted from Ebers G, Lancet Neurol 2008)
# Candidate Genes in MS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosomal position</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>HLA DRB1</em></td>
<td>6p21-6p23</td>
<td>2.3-6.4</td>
</tr>
<tr>
<td><em>IL2RA</em>, interleukin 2 receptor</td>
<td>10p15</td>
<td>1.25</td>
</tr>
<tr>
<td><em>IL7R</em>, interleukin 7 receptor</td>
<td>5p13</td>
<td>1.18</td>
</tr>
<tr>
<td><em>CLEC16A</em>, C-type lectin domain family 16, A</td>
<td>16p13</td>
<td>1.14</td>
</tr>
<tr>
<td><em>RPLS</em>, ribosomal protein LS</td>
<td>1p22</td>
<td>1.15</td>
</tr>
<tr>
<td><em>DBC1</em>, deleted in bladder cancer 1</td>
<td>9q33</td>
<td>1.17</td>
</tr>
<tr>
<td><em>CD58</em>, lymphocyte function-associated antigen 3</td>
<td>1p13</td>
<td>1.24</td>
</tr>
<tr>
<td><em>ALK</em>, anaplastic lymphoma receptor tyrosine kinase</td>
<td>2p23</td>
<td>1.37</td>
</tr>
<tr>
<td><em>FAM69A</em>, family with sequence similarity 69, A</td>
<td>1p22</td>
<td>1.12</td>
</tr>
</tbody>
</table>
Genetic Susceptibility and MS

- Maximal concordance of MS in identical twins is ~30% (in high risk areas)
- Genome wide association studies contribute little in explaining overall MS risk
- Environmental and epigenetic modifications on genome require study
- Susceptibility genes “load the gun”
MS: Risk Factors for Onset

- **Environmental Factors**
  - Geography
  - Infectious trigger
  - Smoking
  - Deficiency of Vitamin D and sunlight
Geography
MS Prevalence in Europe, 1980, by latitude (Kurtzke, 1980)
Service Connection for MS
Title 38 CFR 3.307

7 years

EAD

RAD
MS in US Veterans during 20th Century
Evidence for Environmental Susceptibility in MS

- **Geographic prevalence gradients**
  - Three prevalence zones
    - Low: < 5 per 100K
    - Medium: 5-29 per 100K
    - High: 30+ per 100K

- **High Risk Zones**
  - Western Europe
  - North America
  - Southeast Australia
  - New Zealand

Kurtzke J, 2004
## Migration between birth and EAD on MS

### Risk Ratios in US Veterans of WWII

(Kurtzke J, *Neurology* 1985)

<table>
<thead>
<tr>
<th>Residence at birth</th>
<th>Residence at entry into military duty (by tier of latitude)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>North</td>
</tr>
<tr>
<td>North</td>
<td>1.48</td>
</tr>
<tr>
<td>Middle</td>
<td>1.40</td>
</tr>
<tr>
<td>South</td>
<td>0.70</td>
</tr>
<tr>
<td>Total</td>
<td>1.46</td>
</tr>
</tbody>
</table>
Migration and MS in Alaskan Military Veterans (Wallin M, J Neurol 2009)

- Provide first estimates of MS prevalence in Alaskan white males
- Population: US veterans of Vietnam Era and later cohort (N=5,345)
- Assess risk for MS in migrants to and from Alaska and “lower 48” (Birth place and EAD)
Estimated prevalence rates* per 100,000 population for US white male veterans of Vietnam Era and later military service by birthplace or residence at entry into service (EAD) in Alaska (AK) (Wallin M, *J Neurol* 2009)

<table>
<thead>
<tr>
<th>Birthplace</th>
<th>EAD</th>
<th>N</th>
<th>Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>AK</td>
<td>7</td>
<td>22.35</td>
<td>8.97 - 46.03</td>
</tr>
<tr>
<td>AK</td>
<td>AK</td>
<td>1</td>
<td>3.20</td>
<td>0.08 – 17.80</td>
</tr>
<tr>
<td>“lower 48” US</td>
<td>AK</td>
<td>6</td>
<td>20.63</td>
<td>7.56 – 44.90</td>
</tr>
<tr>
<td>AK</td>
<td>“lower 48” US</td>
<td>9</td>
<td>114.92</td>
<td>52.60 – 218.05</td>
</tr>
</tbody>
</table>

*calculated from prevalence rate of 45.23 for US white males (Baum and Rothschild 1981) times adjusted case/control ratios for each subset divided by adjusted case/control ratio for all white male veterans
Conclusions:

- Alaska is apparently a low risk area for MS
- Migration before onset to Alaska for those born in the coterminous US decreases MS risk
- Migration from Alaska for those born in the coterminous increases MS risk
- Vitamin D hypothesis not supported by data
- A formal MS prevalence survey is required to support or refute these findings
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
Evidence for an infectious cause of MS

- MS Epidemics (Faroe Islands)
- Antibody in cerebrospinal fluid
- Viral related demyelination models (e.g. PML, Theiler’s murine encephalomyelitis virus)

(Gilden D, Lancet Neurol 2005)

Rabies virus (1946)
Herpes simplex virus (1964)
Scrapie agent (1965)
Parainfluenza virus 1 (1972)
Measles virus (1972)
Simian virus 5 (1978)
Chimpanzee cytomegalovirus (1979)
Coronavirus (1980)
SMON-like virus (1982)
Tick-borne encephalitis flavivirus (1982)
HTLV-1 (1986)
LM7 (retrovirus) (1989)
HSV1 (1989)
HHV-6 (1994)

“Absence of evidence is not the same as evidence of absence”
Dyson F, 1981
Epstein Barr Virus and MS Risk
(Thacker E, Ann Neurol 2006)
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 ctls)

<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>
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 sxs
- 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


- Increasing titers of EBNA-1 antibodies in MS cases may be related to another infection
A unifying multiple sclerosis etiology linking virus infection, sunlight, and vitamin D, through viral interleukin-10

Colleen E. Hayes a,*, E. Donald Acheson b

a Department of Biochemistry, University of Wisconsin, Madison, 433 Babcock Drive, Madison, WI 53706, USA
b International Centre for Health and Society, University College London, 1–19 Torrington Place, London WC1E 6BT, UK

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Deployment and DoD-VA Cohorts
1990-1991 Gulf War

- Conflict between Iraq & coalition forces from 34 nations led by US to liberate Kuwait
- Nearly 700,000 US troops deployed to the war theater
- Gulf War Conflict: 8/1/90-7/31/91
- 42 days of combat started January 17, 1991 with 148 US troops killed
- $60-70 Billion to deploy and maintain US troops
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
MS in the Middle East

- Population survey of MS in Kuwait 1993-2000
- Incidence rate increased from 1.05/100,000 in 1993 to 2.62 per 100,000 in 2000
- Prevalence changed from 6.7 to 14.8 per 100,000
- Systemic Review of Middle East prevalence studies: 4-42 per 100,000 (Benamer H, *J Neurol Sci* 2009, Al-Himyari F, Frequency of MS in Iraq, AAN 2009 P09.017)
MS in Gulf War-era Veterans Study Cohort (n=2,691)

3,499 veterans with MS/CIS SC dx and active duty service between 1990-2007

- 2,478 with diagnosis of MS/Possible
- 116 with diagnosis of optic neuritis
- 97 with diagnosis of transverse myelitis/other/CIS NMO
- 561 Not MS/CIS
  - 247 with dx < 1990
GW MS Cohort: Average Annual MS Incidence Rates (Wallin, et al Brain 2012)
GW MS Cohort: Average Annual MS Incidence Rates (Wallin, et al Brain 2012)
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)**
MS Risk Assessment Through the Lifespan

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Protective</th>
<th>Exacerbating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equatorial Latitude</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin-D (diet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UVB exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV, HHV-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other viruses &amp; toxin(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>smoking ??</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vaccines ??</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Prognosticators @ onset of MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
</tr>
<tr>
<td>younger age</td>
</tr>
<tr>
<td>sensory symptoms</td>
</tr>
<tr>
<td>relapsing MS</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>older age</td>
</tr>
<tr>
<td>motor symptoms</td>
</tr>
<tr>
<td>progressive MS</td>
</tr>
<tr>
<td>family HX of MS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MS Disease Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>fewer relapses with full recovery (RRMS)</td>
</tr>
<tr>
<td>shorter disease history</td>
</tr>
<tr>
<td>DMT</td>
</tr>
<tr>
<td>Vitamin-D supplements (UVB exposure) ??</td>
</tr>
<tr>
<td>frequent relapses without full recovery (SPMS)</td>
</tr>
<tr>
<td>primary progressive disease course</td>
</tr>
<tr>
<td>longer disease history</td>
</tr>
<tr>
<td>comorbidities</td>
</tr>
<tr>
<td>smoking ??</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
</tr>
<tr>
<td>QOL</td>
</tr>
<tr>
<td>Disability</td>
</tr>
<tr>
<td>ADLs</td>
</tr>
<tr>
<td>MS Symptoms</td>
</tr>
<tr>
<td>Survival</td>
</tr>
<tr>
<td>Infections - Decubiti - UTI - Pneumonia</td>
</tr>
<tr>
<td>DVT / PE</td>
</tr>
</tbody>
</table>

NOTE: Items displayed in BLUE are EFFECT MODIFIERS that can vary naturally (e.g., living at a southern latitude) or are modifiable (e.g., smoking, DMT use). A "??" is placed next to those items that have been suggested, but not conclusively demonstrated, to impact MS risk or outcomes.
MS Risk Factors for Onset

Conclusions

- Geography and EBNA-1 Abs are significant MS risk factors
- Environmental risk factors require validation in larger, ethnically diverse cohorts
  - Interaction between risk factors
  - Gene-environmental interaction
- Prevalence hypothesis for an infectious trigger in MS has the most plausibility from the epidemiologic data:
  - Migration data (high to low risk, low to high risk)
  - Faroe Islands Type 1 Epidemic
  - Novel infectious agents should continue to be explored
- Join the Marines!
MSCoE Epidemiology Research Group

- **VA MSCoE**
  - Parisa Coffman, MPH
  - Heidi Maloni, PhD
  - Joel Culpepper, PhD
  - Jodie Haselkorn, MD, MPH
  - John Kurtzke, MD

- **VA Environmental Epidemiology**
  - Han Kang, PhD
  - Clare Mahan, PhD

- **NIH-NINDS**
  - Steve Jacobson, PhD

- **DoD Serum Repository & WRAMC/DoD Neurology**
  - Mark Rubertone, MD
  - Daniel Correa, MD
  - Steve Lewis, MD
  - Anthony Frattalone, MD
  - Angie Eick, PhD

- **Johns Hopkins University/Welch Ct**
  - Joseph Finkelstein, MD, PhD

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