Multiple Sclerosis: Risk Factors for Onset

May 29, 2015
CMSC Annual Meeting
Indianapolis, IN

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

Veterans Affairs MS Center of Excellence East

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

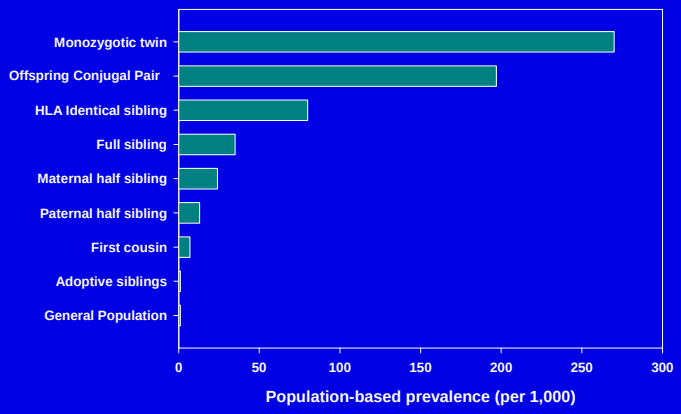
Evidence for Environmental Susceptibility in MS

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

Broad Street Pump, London
150th Anniversary J. Snow *MMWR* 2004 53:783

Familial Aggregation and MS Risk

(adapted from Ebers G, *Lancet Neurol* 2008)



Candidate Genes in MS

(adapted from Baranzini S, *Curr Opin Neurol* 2012)

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

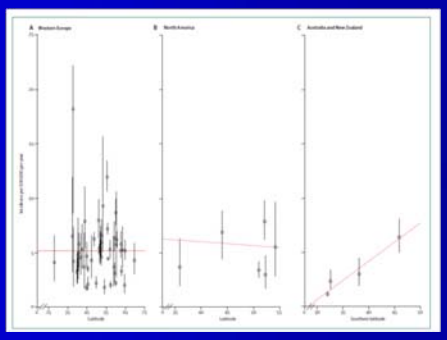
Genetic Susceptibility and MS

- 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”

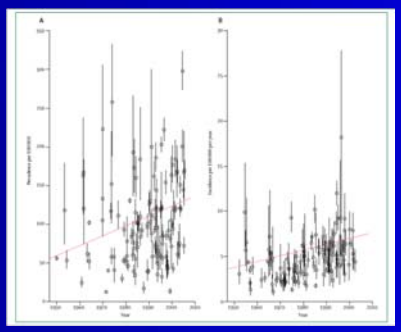
Geography

MS Prevalence & Incidence Trends

(Koch-Henriksen, *Lancet* 2010)

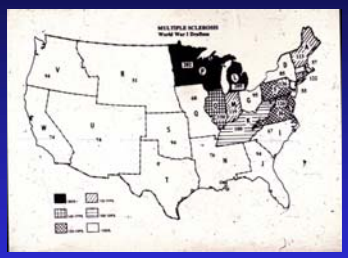


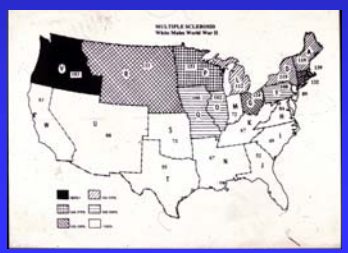
Incidence vs Latitude

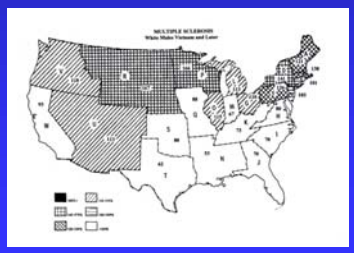


Incidence vs Time

MS in US Veterans during 20th Century







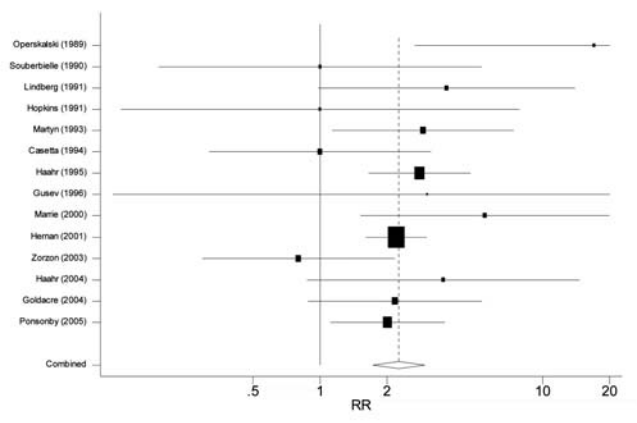
Infectious Triggers

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)



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)

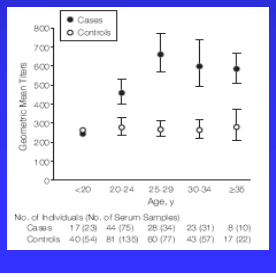
Antibody	*Bivariate Analysis RR (95% CI)*	*Multivariate Analysis RR (95% CI)*
EBV-EBNA-1	4.2 (1.9-9.2)*	4.5 (1.9-11)*
EBV-VCA	1.1 (0.57-2.3)	0.86 (0.38-2.0)
HSV	0.63 (0.32-1.2)	0.59 (0.25-1.4)
VZV	1.1 (0.60-2.2)	0.94 (0.44-2.0)
Measles	2.4 (1.1-5.6)*	1.4 (0.52-3.6)
HHV-6	2.4 (1.2-4.8)*	2.3 (1.0-5.1)*

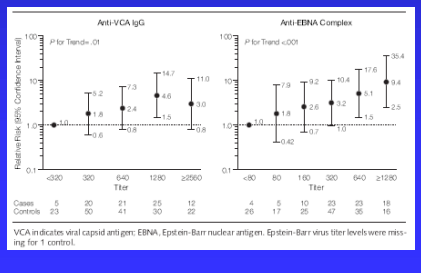
EBV Antibody titers and MS Onset

(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



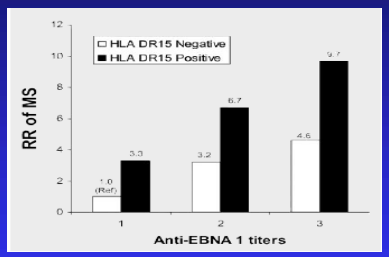


HLA and EBV in risk of MS

(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-

Relative Risk of MS
by anti-EBNA-1 titers & HLA D15 status



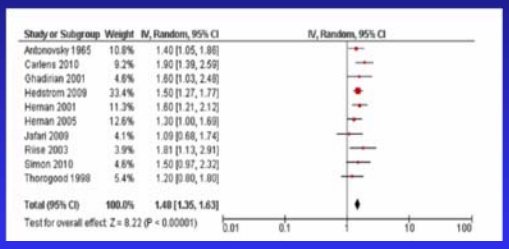
EBV as a candidate virus in the etiology of MS

- 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

(Handel, *PLoS One*, 2012)



- 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

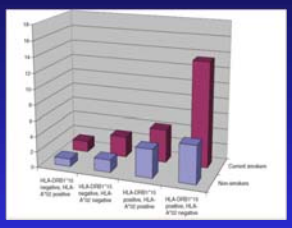
(Hedstrom, *Eur J Epidemiol* 2013 & *Neurology* 2009)

Swedish population-based case-control studies

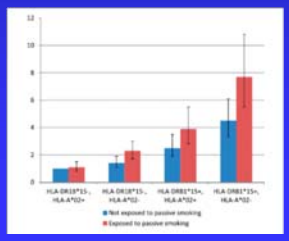
- Clear dose-response relationship between smoking and MS onset
- Detrimental effects abate after 10 years of smoking cessation
- No clear relationship between age of onset and risk for MS
- Use of Swedish snuff tobacco not associated with increased MS risk

Effects of Smoking & HLA Genes on MS Risk (Hedsrom, et al *Brain* 2011 and *Int J Epid* 2014)

Active smokers



Passive smokers



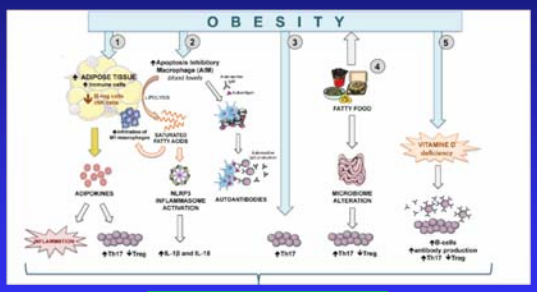
- The risk of developing MS associated with different HLA genotypes is influenced by both active and passive smoking
- Active smokers: Compared with non-smokers with neither of the genetic risk factors, the odds ratio was 13.5 (8.1–22.6) for smokers with both genetic risk factors
- Passive smokers: Non-exposed 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)

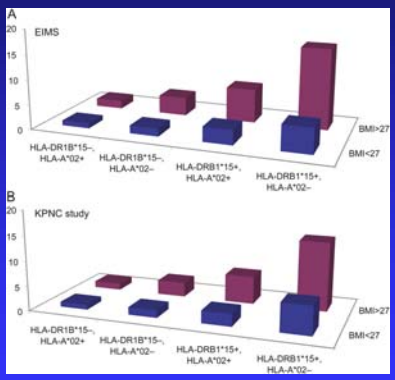
Obesity & Mechanisms for Immune Activation (Versini, 2014)



Immune Activation

- 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

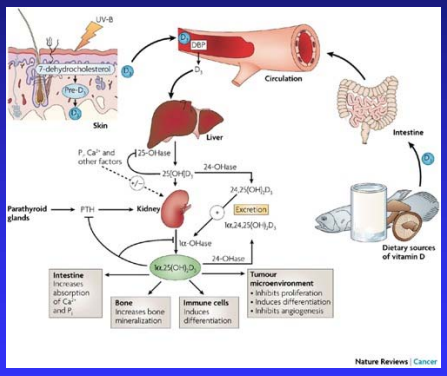
Interaction among adolescent obesity, carriage of HLA-DRB1*15 (Hedstrom, *Neurology* 2014)



- 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

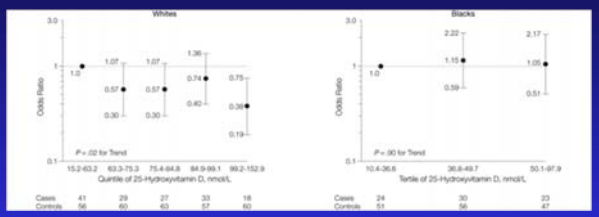
Vitamin D and MS Risk

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 neurotransmiters
  - Neuroprotection in glutamate-induced cell death of cortical neurons in animal models

Vitamin D & MS Risk



Munger K, *JAMA* 2006

- 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.

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

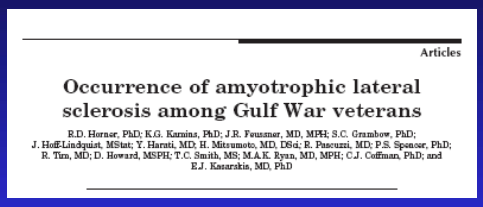
Military Deployment and MS Risk

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

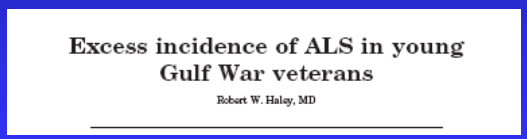
(Neurology, September 2003)



Articles

Occurrence of amyotrophic lateral sclerosis among Gulf War veterans

R.D. Horner, PhD; K.G. Kamins, PhD; J.R. Feussner, MD, MPH; S.C. Grambow, PhD; J. Hoff-Lindquist, MStat; Y. Harati, MD; H. Mitsumoto, MD, DSc; R. Pascuzzi, MD; P.S. Spencer, PhD; R. Tim, MD; D. Howard, MSPH; T.C. Smith, MS; M.A.K. Ryan, MD, MPH; C.J. Coffman, PhD; and E.J. Kasarskis, MD, PhD



Excess incidence of ALS in young Gulf War veterans

Robert W. Haley, MD

- 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