

Multiple Sclerosis & Gulf War Veterans

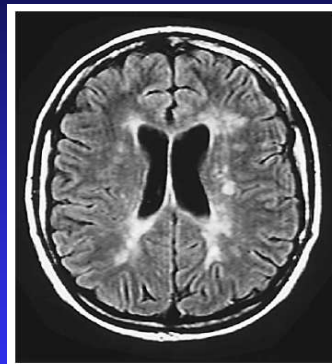
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Jodie K. Haselkorn, MD, MPH

Director, MS Center of Excellence West-Seattle
Professor, Department of Rehabilitation Medicine
Adjunct Professor, Epidemiology
University of Washington

Multiple Sclerosis

- Clinical disorder
- No cause or cure
- Immune mediated
- Inflammatory
- Demyelization
- Axonal loss
- Affects the brain and spinal cord
- Acute or insidious
- Frequently progressive
- Common neurological disease with onset in 20s-40s
- 350,000-400,000 people with MS in the US



Axial FLAIR Brain MRI (NEJM, 2000)

Diagnosis of MS: Established Criteria

- History & Physical Exam
- Paraclinical Evidence
 - ◆ CSF
 - ☞ Elevated IgG index
 - ☞ Presence of oligoclonal bands in CSF & not in serum
 - ◆ Evoked potentials (visual, auditory, somatosensory)
 - ☞ Looking for slowed conduction described as prolonged evoked response latency
 - ◆ MRI
- Exclusion of other diagnoses

McDonald WI, *et al.*, 2001.
Polman CH, *et al.*, 2005.

Some Invisible and Visible Impairments in MS

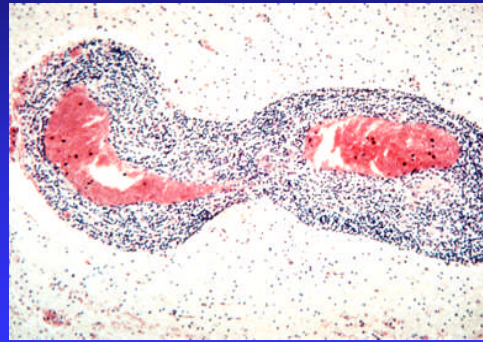
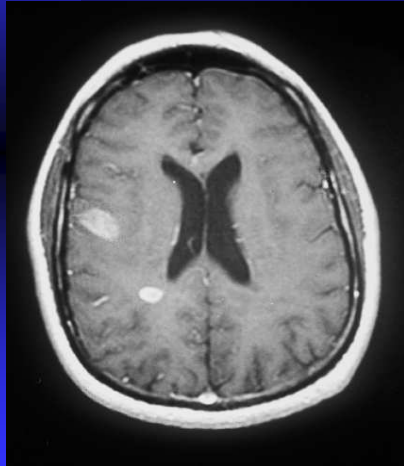
Invisible

- Fatigue
- Mood Disorders
- Sensory Impairments
- Visual Changes
- Cognitive Impairments
- Bladder/Bowel Disorders
- Sleep Disorders
- Medication side effects

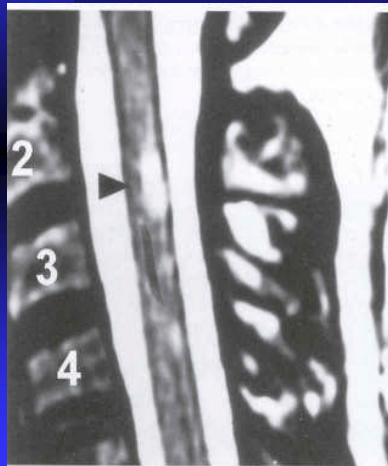
Visible

- Communication
- Motor Impairment
- Tremor/Ataxia
- Balance
- Hearing Disorders

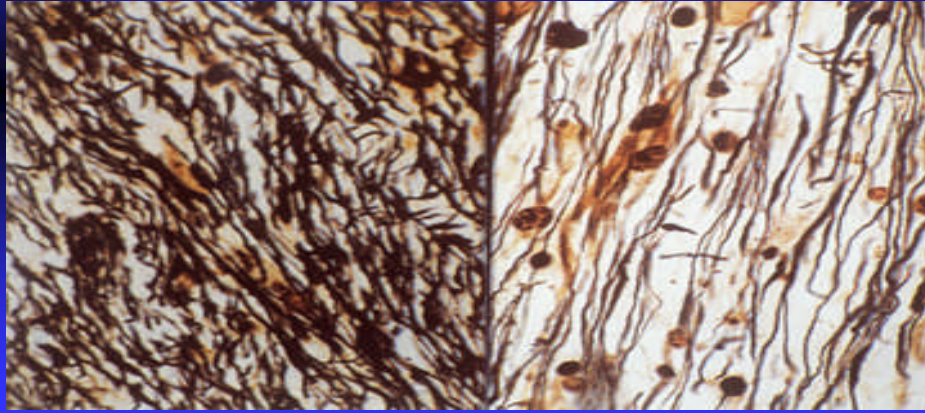
Active Inflammation in MS: Symptoms Relate to Inflammation



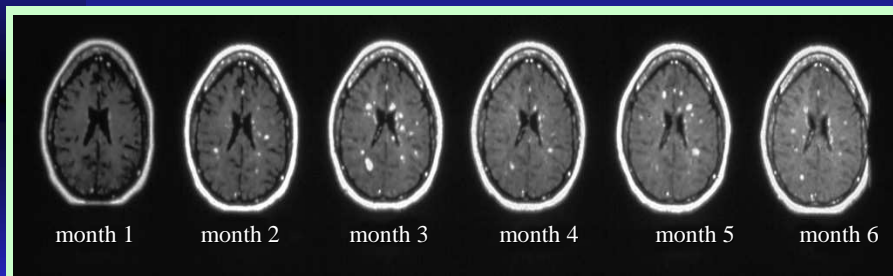
Demyelization: Symptoms Associated with Demyelization



MS and Axonal Injury: Symptoms Relate to Axonal Loss



Serial Monthly MS Enhancing Lesions: Symptoms May Not Relate to Disease Activity



History of Multiple Sclerosis

- 1868 - Jean-Martin Charcot described the pathology “sclerose en plaque”
- No known etiology
 - ◆ Immunology
 - ◆ Genetics
 - ◆ Infectious
 - ◆ Environmental
- Treatment is available
 - ◆ Disease modification
 - ◆ Symptom management

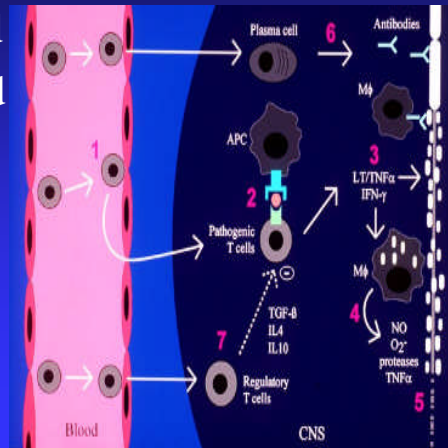


Current Theory

Abnormal immune response to
an infection or environmental trigger
in a genetically susceptible individual

MS Immunology

- T-cell mediated
- B-cell mediated



MS Genetics

- Susceptibility
 - ◆ Major Histocompatibility Complex, Chromosome 6
 - ◆ Interleukin-2 receptor-alpha
 - ◆ Interleukin-7 receptor-alpha
 - ◆ TOB1
 - ◆ others
- Protection
 - ◆ HLA-C*05 and others may be protective
- Polygenic disorder
- Gender effect in susceptibility and transmission
- Complex gene-environmental interactions
 - ◆ 30% concordance in monozygotic twins

Infectious Etiology MS: Premises

- Epidemiological evidence of childhood exposure to infectious agents and increase in disease exacerbations with viral infection
- Geographic association of disease susceptibility with evidence of MS clustering
- Evidence that migration to and from high-risk areas influences the likelihood of developing MS
- Abnormal immune responses to a variety of viruses
- Viruses cause diseases with long incubation periods, a relapsing-remitting course, and demyelization in animals and humans

MS Infectious Etiology: 2 Theories

- MS is a rare complication of a widespread microbe
 - ◆ Prevalence hypothesis
 - ☞ MS is triggered by a microbe more common in geographic regions of high risk
 - ◆ Hygiene hypothesis
 - ☞ MS is triggered by a late age infection of a common microbe

Support for Infectious Trigger

- Epstein-Barr virus and MS in military 1988-2000 strong association with high titers of EBV prior to development of MS
Levin, 2003.
- Presence in 21/22 brain specimens from individuals with MS, but not 0/7 specimens from individuals who had other neurological disorders
Serafini, 2007.
- HLA DR15 and increased serum antibodies to EBV much more likely to develop MS than those with high titers alone
De Jager, 2008.

Evidence for Environmental Susceptibility in MS

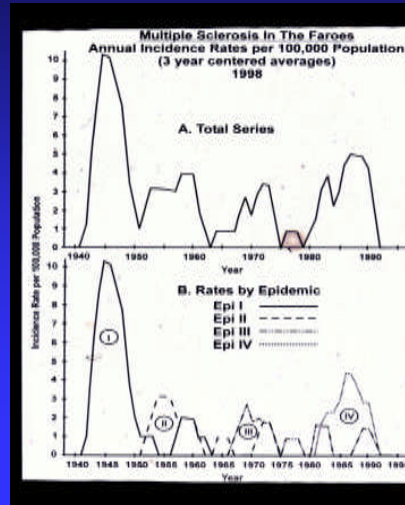
- Geographic prevalence gradients
 - ◆ Three prevalence zones
 - Low: < 4 per 100K
 - Medium: 5-29 per 100K
 - High: > 30 per 100K
- High Risk Zones
 - ◆ Europe
 - ◆ North America
 - ◆ So. Australia
- Migration from one zone to another changes risk



Kurtzke, 2004

Evidence for Environmental Susceptibility in MS

- Epidemics of MS
 - ◆ Faroe Islands
 - ◆ Other clusters



MS in Gulf War: Kuwait Population Survey 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
- Most dramatic changes seen in Kuwaiti natives

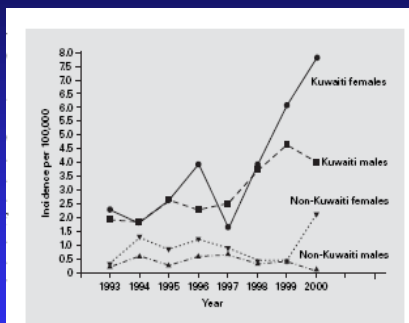


Fig. 1. Incidence of MS in Kuwait according to sex and nationality, 1993-2000.

Alshubaili, Eur Neurol 2005

Immediate Neurological Morbidity and Gulf War Veterans

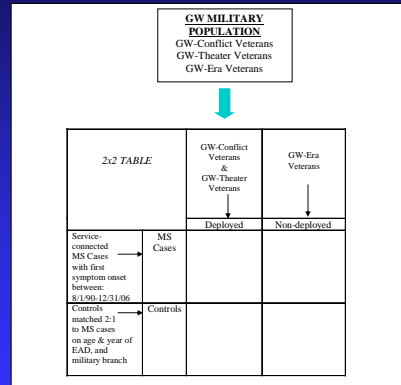
- Large population-based studies show no differences in neurological exam findings or NCS between GW veterans and controls
Bourdette, 2001; Sharief, 2002; Davis, 2004; Rose, 2004; Eisen, 2005; Kelsall, 2005
- Diagnostic evaluations in 16 studies show neurologic function was normal in most cases
Rose, 2006
- Small proportion of GW veterans diagnosed with compression neuropathies
Davis, 2004; Eisen 2005

MS in Gulf War Veterans Study: Specific Objectives

- Identify onset and clinical subtype on all GW MS service-connected cases between 1990-2006 in the GW military population.
- Quantify risk for MS in GW veterans deployed to the combat theater compared with non-deployed.
- Quantify risk in GW veterans with known exposures using existing databases and statistical models.

MS in Gulf War Veterans Study: Hypotheses

- Primary Hypothesis:
 - ◆ Deployed GW veterans will be at increased risk for MS compared with non-deployed GW veterans
- Secondary Hypothesis
 - ◆ In-theater exposure characteristics of deployed GW veterans will be associated with an increased risk of MS



Potential Risk Factors for MS in Gulf War Veterans

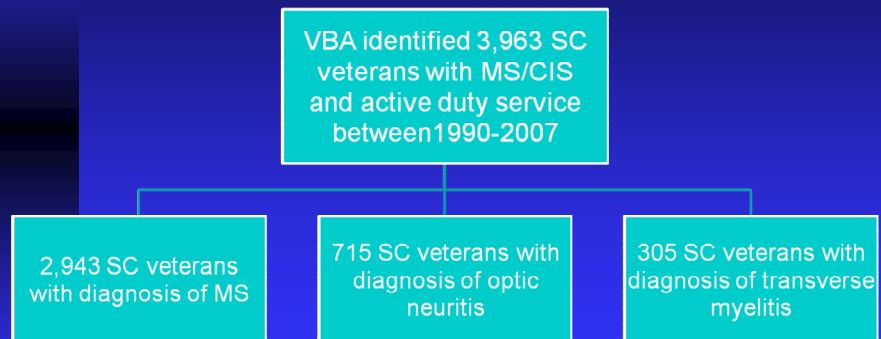
- Vaccinations
 - ◆ Anthrax (Kerrison, 2002)
 - ◆ Hepatitis B (Hernán, 2004)
- Viral infections
 - ◆ Parvovirus B19 aplastic crisis 1991 in Gulf region (Mallouh, 1995)
- CNS toxins
 - ◆ Sarin
 - ◆ Pyridostigmine bromide
 - ◆ Organic solvents (Riise, 2002)
- Air pollutants (Oikonen, 2003)



MS in Gulf War Veterans Study

- Case-control study design: 2 pre-illness military controls matched to each MS service-connected case on:
 - ◆ age and date of entry into active duty
 - ◆ service branch
- Deployed GW veterans will be at increased risk for developing MS compared with non-deployed GW veterans:
 - ◆ OR stratified by demographic & clinical variables
 - ◆ Logistic regression analysis
 - ◆ Kaplan-Meier curve to assess 15-year risk of developing service-connected MS diagnosis (deployed vs. non-deployed)
- In-theater exposure characteristics of deployed GW veterans will be associated with an increased risk of developing MS.
 - ◆ Logistic regression analysis based on existing troop models of exposure

MS in Gulf War Veterans Study Cohort

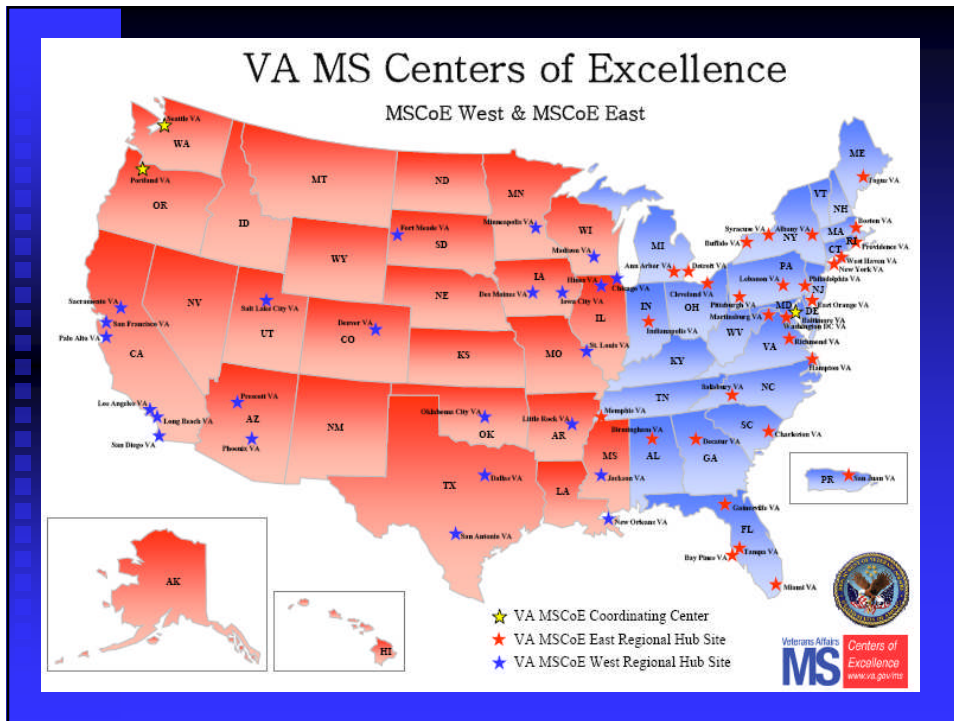


MS Centers of Excellence: Mission

- **Consistent, high quality health care to all veterans with MS**
 - ◆ Interdisciplinary
 - ◆ Integrated
 - ◆ Evidence based

Chronic Care Model

- **Assure the delivery of effective, efficient clinical care and self-management support**
- **Promote clinical care that is consistent with scientific evidence and veteran preferences**
- **Organize data to facilitate efficient and effective care**



MS Center of Excellence: Clinical Care

■ Clinical Care

- ◆ Increase allocation of funds to facilities
- ◆ Developed a Standards of Care Manual
- ◆ Developed a Regional network
- ◆ Share best practices
- ◆ Set up a natalizumab database with the MS Repository for monitoring adverse events

MS Center of Excellence: Education

- Satellite broadcasts
- Symposium and 2 workshops at International Meeting of the Consortium of MS Centers
- Annual Whitaker lecture
- Regional education
- Dystel nursing education to build MS nursing capacity
- Monthly physicians, nurses and veteran calls
- Website

MS Centers of Excellence: Informatics

- Built and maintain the VA National MS Repository
- Built and maintain website www.va.gov/ms
- Electronic Medical Record Enhancements
- Telehealth

MS Center of Excellence: Research

- Basic
- Clinical
- Epidemiological and Health Services Research

Team Members for Veterans with MS:

- | | |
|---------------------------------|----------------------------|
| ■ Primary care provider | ■ Occupational Therapy |
| ■ Neurologist | ■ Pain Management |
| ■ Psychiatrist | ■ Physical Therapy |
| ■ Pharmacy | ■ Prosthetics |
| ■ Long term Care | ■ Recreation Services |
| ■ Mental Health | ■ Social Work |
| ■ Nursing-MS and Rehabilitation | ■ Speech and Communication |
| | ■ Vocational Services |

MS in Gulf War Veterans: Summary

- MS is a well described disease with established diagnostic criteria
- MS results in invisible and visible impairments
- The etiology of MS is unknown so we can not evaluate a single exposure
- VA is doing research on quantifying the risk in GW veterans
- MS Center of Excellence is committed to providing high quality care, consistent care to GW and all other veterans with MS