Multiple Sclerosis & Gulf War Veterans
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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

Polman CH, et al., 2005.

Some Invisible and Visible Impairments in MS

<table>
<thead>
<tr>
<th>Invisible</th>
<th>Visible</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>Communication</td>
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<td>Mood Disorders</td>
<td>Motor Impairment</td>
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<td>Sensory Impairments</td>
<td>Tremor/Ataxia</td>
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<td>Visual Changes</td>
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<td>Cognitive Impairments</td>
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<td>Bladder/Bowel Disorders</td>
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<td>Sleep Disorders</td>
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<td>Medication side effects</td>
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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

- Presence in 21/22 brain specimens from individuals with MS, but not 0/7 specimens from individuals who had other neurological disorders

- HLA DR15 and increased serum antibodies to EBV much more likely to develop MS than those with high titers alone

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

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-Meir 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

- VBA identified 3,963 SC veterans with MS/CIS and active duty service between 1990-2007
- 2,943 SC veterans with diagnosis of MS
- 715 SC veterans with diagnosis of optic neuritis
- 305 SC veterans with diagnosis of transverse myelitis
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
- Neurologist
- Psychiatrist
- Pharmacy
- Long term Care
- Mental Health
- Nursing-MS and Rehabilitation
- Occupational Therapy
- Pain Management
- Physical Therapy
- Prosthetics
- Recreation Services
- Social Work
- 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 cannot 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