Occurrence of ALS among Gulf War Veterans: Using the Epidemiology as a Guide to Intervention

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Presentation Objectives

- Review Current Understanding of the Epidemiology of ALS among Gulf War Veterans
- Present Current Thoughts on the Emerging Evidence Relevant to the Etiology of the Outbreak (and hence Mechanism and Intervention)

I. Overview
Clinical Description of ALS

- A neuro-degenerative disease involving the death of motor neurons
- Invariably terminal with death typically occurring within 2-5 years post-onset
- Incidence increases with age, especially after 55 years of age
- Etiology is uncertain, although 10% of cases have a familial history

Unique Aspects of the ALS Cluster among 1991 Gulf War Veterans

- Relatively Young Men Affected (i.e., approximately 50% of cases under 25 years of age at onset)
- Individuals Fit for Combat (i.e., Healthy Warfighter Effect – Expected Rate below that of the General Population)
- Family History of ALS in ~10% of Cases (3 of 40 cases in original cohort)
- One of Largest Contemporary Clusters of Cases
**Intervention Through Epidemiology**

- Current Cluster Represents an Unusual Occurrence
- Epidemiologist Study High-risk or Unusual Outbreaks to Discover Etiology
- Etiologic Knowledge may Suggest the Mechanism by which the Agent Exerts Its Effect
- Mechanism May Point to Therapies

**II. Brief Review of the Epidemiology of the 1991 Gulf War Outbreak**
### Reports on Occurrence of ALS among 1991 Gulf War Military Personnel

<table>
<thead>
<tr>
<th>Study</th>
<th>Case Ascertainment Time Period</th>
<th>Number of ALS Cases: Deployed</th>
<th>Number of ALS Cases: Non-deployed</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith, 2000</td>
<td>1991 - 1997</td>
<td>6</td>
<td>12</td>
<td>1.66 (0.62, 4.44)</td>
</tr>
<tr>
<td>Horner, 2003</td>
<td>1990 - 2000</td>
<td>40</td>
<td>67</td>
<td>1.92 (1.29, 2.84)</td>
</tr>
<tr>
<td>Coffman, 2005</td>
<td>1990 - 2000</td>
<td>42*</td>
<td>76*</td>
<td>1.77 (1.21, 2.69)</td>
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<tr>
<td>Horner, 2008 Update</td>
<td>1991 - 2001</td>
<td>48</td>
<td>76</td>
<td>1.90 (1.34, 2.69)</td>
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<tr>
<td>Barth, 2009</td>
<td>1991 - 2004</td>
<td>23</td>
<td>38**</td>
<td>0.96 (0.56, 1.62)</td>
</tr>
</tbody>
</table>

* Best estimate from capture-recapture analysis  ** Based on 50% sample of non-deployed

### Why So Few ALS Deaths among Deployed in Barth et al. ?

- **Definition of Study Population?**
  - Deployment: 8/1/90 – 3/31/91 vs. 8/2/90 – 07/31/91
  - Result: N=621,902 vs. N=696,118 (∆=74,216)
  - Non-deployed: 50% sample so equivalent to other studies

- **Definition of Case?**
  - Motor Neuron Disease (335.2) or ALS (335.20)
**Epidemic Curve for Deployed Military Personnel (vs. Non-deployed Military)**

- **Solid Line:** All Cases
- **Dashed Line:** Cases under 45 yrs of age at onset
- **Expected cases:** Non-deployed military personnel

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</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Horner et al. *Neuroepidemiology* 2008; 31: 28-32

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**Descriptive Epidemiologic Studies**

- No Persian Gulf Variant of ALS is Apparent (Dr. Kasarskis)
  - Shorter survival for Deployed versus Non-deployed Cases

- No Known Data on ALS as Endemic or Epidemic in Native Middle East Populations
**Survival of ALS Cases by Deployment Status: A Distinguishing Characteristic**

![Graph showing survival curves for ALS cases by deployment status.](graph.png)

Survival curves adjusted for age and type: bulbar vs. non-bulbar. Kasarskis et al. ALS, 2008; 16: 1-7

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

*Source: Alshubaili et al, Eur Neurol 2005; 53: 125-131*
III. Update on the Inquiry into the Etiology of the Outbreak

Quest for Clues to the Etiology

- Military Service as a General Risk for ALS (Dr. Weiskopf)
- Sartwell’s Model to Assess Likelihood of Common Source or Common Time Point of Exposure
  - Shape of Cumulative Distribution of Case Onset
- GIS Analysis of Spatial “Hot Spots” in the Theater of War (Dr. Miranda)
  - Common Points of Exposure in Geographical Space (and Time)
Why Military Service Does Not Explain the 1991 Gulf War Outbreak

- Weiskopf Study: Higher risk of ALS among those with any military service.
  - Overall risk: 1.53 (95% CL = 1.12, 2.09); Highest risk: Army and Navy, but not Air Force
  - Increasing risk with increasing number of wars during military service; no association with years of service
  - Population was older individuals: Mean age was 64.7 yrs for “Never Served” versus 62.8 years for “Served”
  - Horner Study: Approx. 50% under 25 yrs of age; 98% under 55 yrs of age

Military Service and ALS Risk: Evidence from a Civilian Population

- W. Washington State Study: Additional Evidence?
  - Half of the men had served in the military
  - Observed rate: 2.12 per 100,000 per year
  - Anecdotal report: 2-fold greater risk among men who had served in military
  - If 2-fold risk with military service, observed rate is an average; “civilian” rate enhanced by 50%
  - Comparison of enhanced civilian rate to military rate should “drive” risk ratio toward the null
**“Epidemic Curve” for Non-Deployed Military Personnel vs. W. Washington State Men**

![Graph showing epidemic curve]

Horner et al. Neuroepidemiology 2008; 31: 28-32

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**Assumptions of Sartwell’s Model**

- Multiplicative (growth) Process in Pathogenesis of Agent or Toxic By-products
  - Threshold at which Symptoms Appear
  - Incubation Period = Time from Symptom Onset – Time of Exposure

- Inherent Individual Variation in Incubation Period

- Functional Form of Onset Distribution Independent of Incubation Period Length and Agent Dosage

- A Lognormal Distribution Infers:
  - Common Source of Exposure
  - Common Time of Exposure
**Distribution of Time of Onset Among All Deployed ALS Cases**

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<td>W-Sq</td>
<td>0.091</td>
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<td>Anderson-Darling</td>
<td>A-Sq</td>
<td>0.042</td>
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**Distribution of Time of Onset Among Deployed ALS Cases <45 yrs at Onset**

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Unpublished data
**Spatial GIS Findings on Potential Etiologic Agents**

- Elevated Risk Associated with Khamisiyah: OR = 1.7 (95% CL = 0.7, 3.7)
- Exposure to Oil Well Fire Smoke not Modeled
- Current Effort is a Spatio-temporal GIS Analysis
  - Determine if Exposures Match in Time as well as Space
  - Model the Oil Well Fire Smoke Exposure

**Other Potential Causes of Outbreak**

- Exposure to Cyanobacteria which Produce Neurotoxic BMAA (Cox et al. Amyotrophic Lat Sclerosis 2009, Suppl 2: 109-117)
- Neurotoxicity via Heavy Metals in Desert Soil (Based on Conversations with Capt. Mark Lyles, DMD, PhD)
- Head Trauma (Schmidt et al. J Neurol Sci 2010; 291: 22-29)
**Adjuvants in Anthrax Vaccine and Motor Neuron Death**

- Murine Model: Adjuvants Injected at Doses Equivalent to Those Received by US Military
- Progressive Decrease in Strength (~50% of strength of controls) via “hang time” Test
- Cognitive Deficits: 4.3 errors per trial vs. 0.2 errors in Water Maze
- 35% Loss of Motor Neuron and 350% Increase in Astrocytes in Spinal Cord


**Gulf-specific Environmental Exposures**

- Exposure to Cyanobacteria which Produce Neurotoxic BMAA (Cox et al. *Amyotrophic Lat Sclerosis* 2009, Suppl 2: 109-117)
  - Cyanobacteria produce beta methylamino-L-alanine
  - “Mats” and “Crusts” wide-spread in Deserts of Qatar and yield BMAA in Dust
- High Concentrations of Heavy Metals in Desert Soil of Kuwait and Iraq (Per Conversations with Capt. Mark Lyles, DMD, PhD)
Lead, Head Trauma and ALS in Military Veterans

- **Lead and ALS** (Fang et al. Am J Epidemiol 2010; 171: 1126-1133)
  - Blood Lead Levels Higher in 184 Cases vs. 194 Controls with Doubling of Blood Lead: Risk of ALS 1.9 (95% CI=1.3-2.7)

- **Head Trauma and APOE-4** (Schmidt et al. J Neurol Sci 2010; 291: 22-29)
  - In 241 Cases and 597 Controls: ALS Odds=2.33 (95% CI=1.18-4.61) if Injury within Prior 15 yrs
  - Strongest Risk in APOE-4 Carriers

Further Thoughts on the Etiology

- **Dose-Response or Threshold Effect?**
  - Multiple Exposures to One Agent
  - Exposures to Multiple Agents
  - Rapid Time to Toxic Dose

- **Agent or Mechanism: Which is Most Salient?**
  - Human Body has Limited Arsenal to Deal with Exposures
  - E.g., 8-10 liver enzymes to metabolize most drugs
Thoughts on the Mechanism

- Could the Pathology of Neurodegenerative Conditions Reflect a Common Mechanism to Protect Neurons:
  - Detoxification of Neuro-toxicants
  - Anti-Oxidative Stress
  - Anti-Inflammation
  - Anti-Apoptosis

- Is there Genetically Mediated Variation in Neuro-protective Response to Neuro-toxicants?

IV. Concluding Thoughts
Evidence and Next Steps

- 2-fold Higher Risk of ALS among 1991 Gulf War Veterans
- Elevated Risk Probably Not Explained by Methodological Biases
- Etiology Remains Uncertain; Exposures Immediately Prior to or During Deployment May Be Involved
- Perhaps It Will Be More Useful to Focus on Mechanism vs. Specific Etiologic Agent(s)