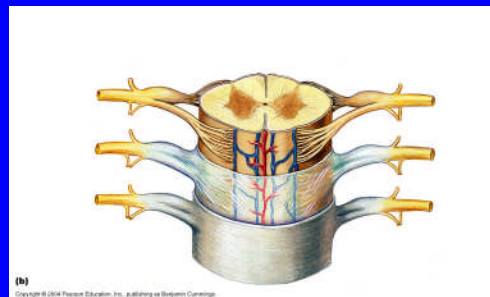


Amyotrophic Lateral Sclerosis and Gulf War Veterans

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Amyotrophic Lateral Sclerosis (ALS)

- **Amyotrophy** – Muscle wasting or atrophy
- **Lateral Sclerosis** – Degeneration and fibrosis of lateral motor pathways of spinal cord.
- a.k.a. Lou Gehrig's Disease (U.S.)

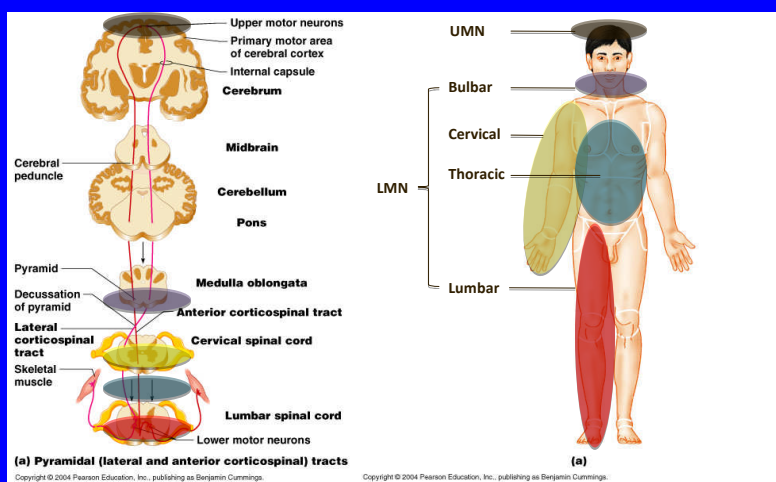


ALS and all Veterans

- Apr. 2003 – VA establishes national registry (CSP #500A) for veterans with ALS and actively enrolls patients over a 4.5 year period. Study enrollment ends Sept. 2007.
 - 2,068 veterans enrolled.
 - 995 still living at end of enrollment period.
 - 1,573 consented to participate in DNA bank.
 - Registry data available to both VA and non-VA investigators through data use requests.
 - 14 studies approved to use registry data for epidemiological, observational and interventional protocols.

Allen et al., Neuropidemiology 2008

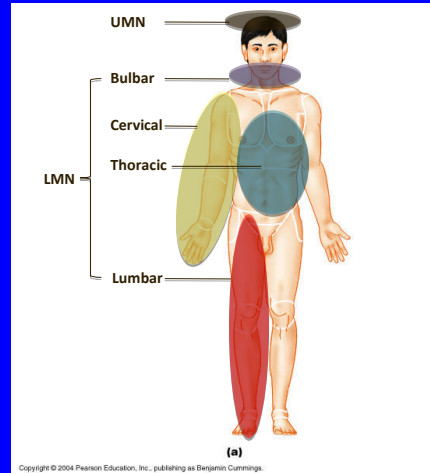
ALS – What is It?



- Progressive loss of upper (UMN) and lower motor neurons (LMN)
- Diagnosis based on constellation of clinical findings (revised El-Escorial criteria)

ALS – Diagnosis

- Revised El-Escorial (Arlie House) Diagnostic Criteria:
- Clinically Definite ALS:
 - 3/4 Body Segments with UMN/LMN Exam Findings
- Clinically Probable ALS:
 - 2/4 Affected Body Segments
- EMG-Laboratory Supported Probable ALS:
 - 2/4 Body Segments with Active Denervation and Chronic Reinnervation.



Brooks BR et al., Arch of Neurol 1996

ALS in the General Population – Epidemiology

- Cumulative lifetime risk 1 in 1,000 for those reaching adulthood. Incidence similar to multiple sclerosis but prevalence much lower due to high mortality.
- 10% of cases hereditary/genetic
- Most common age of onset between 40-60 yrs.
- Male/Female ratio 1.5:1
- Median time to death 2-4 years although 10% of patients survive greater than 10 yrs.
- Riluzole only FDA approved medication to prolong life in ALS patients by about 3 months.

Distad BJ, Meekins GD et al., Phys Med Rehabil Clin N Am 2008
Schmidt et al., Neuroepidemiology 2008

ALS in the General Population – Epidemiology

- **Potential Risk Factors:**
 - High Fat/Glutamate, Low Carb Diet
 - Smoking
 - Slimness and athleticism
 - Urban living

Distad BJ, Meekins GD et al., Phys Med Rehabil Clin N Am 2008

ALS and the General Population – Potential Causes

- Exact disease mechanism unknown
- Likely multifactorial
- Possible contributors:
 - Susceptibility genes
 - Excitotoxicity
 - Apoptosis (programmed cell death)
 - Oxidative stress and mitochondrial dysfunction
 - Neuroinflammation
 - Protein aggregation

Distad BJ, Meekins GD et al., Phys Med Rehabil Clin N Am 2008

ALS and Gulf War Veterans (GWV) Timeline

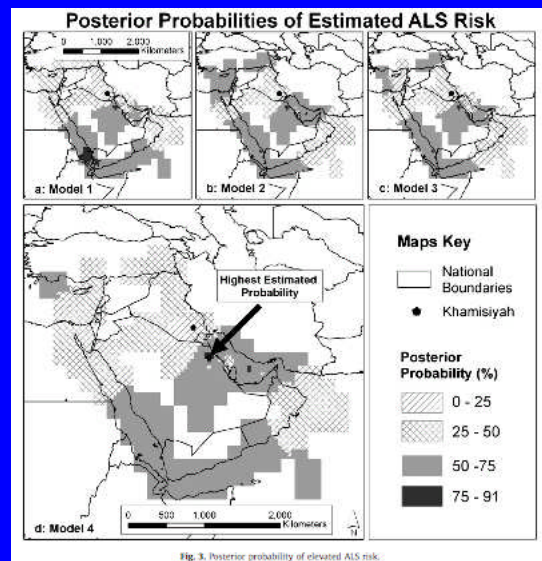
- August 1990-July 1991 – 700,000 million service personnel in SW Asia Theater for Operations Desert Shield/Storm.
- 1990's – Young GWV in 3rd-4th decades of life diagnosed with ALS (typical onset 5th-7th decades).
- 1999-2000 – VA/DOD study of 2.5 million veterans, case rate for ALS in deployed GWV 6.7/million persons/year vs. non-deployed case rate 3.5/million persons/year (n=1.8 million) suggesting a statistically elevated risk of ALS in the GWV group (RR = 1.92; 95% CL = 1.29, 2.84) (Horner et al., Neurology 2003).

ALS and GWV Timeline

- Dec. 2001 – VA Secretary Anthony Principi announced connection between Gulf War service and ALS, conferring full disability and survivor benefits to Gulf War Veterans with ALS.

ALS and GWV

- Higher observed incidence of ALS vs. expected incidence in Gulf War Veterans (Haley , Neurology 2003). Horner study findings confirmed on post-hoc capture-recapture analysis. (Coffman et al., Neuroepidemiology 2005)
- Highest observed risk occurred 1996 and declined thereafter. “The excess risk of ALS among 1991 Gulf War veterans was limited to the decade following the war.” (Horner et al., Neuroepidemiology 2008)



Miranda et al., Neurotoxicology 2008

ALS and all Veterans

- 2005 – Prospective study reports increased ALS mortality for veteran (n=281,874) vs. non-veteran male population (n=126,414) (RR=2.24, CI: 1.12-2.09) (Weisskopf et al., Neurology 2005)
- Nov. 2006 – Institute of Medicine report concludes “limited and suggestive evidence of an association between military service and development of ALS”.
- Sept. 2008 – VA Secretary James Peake announces ALS a service connected condition for all affected veterans with ≥ 90 day service.

Future Study

- **Oct. 2008** - *ALS Registry Act* signed into law by President George Bush establishing a national, CDC-sponsored ALS patient registry for the U.S. general population with a mandated, two-year funding period.
 - \$25 Million for fiscal 2009-2009 and \$16 Million as needed for fiscal 2010-2012.

Conclusions

- GW service is associated with an increased risk of developing ALS but evidence suggests this excess risk was limited to the decade after the war.
- The cause of ALS in GWV is unknown.
- Unclear if GWV have elevated long-term risk of ALS compared to non-deployed veterans or the general population.
- Further study of cluster and genetic data from GWV with ALS may identify environmental triggers and susceptibility genes.

Recommendations

- Long-term surveillance of GWV for adverse health events and development of a sentinel system to alert VA healthcare providers of potential future symptom/disease outbreaks.
- Study of VA healthcare delivery for veterans with ALS. Are they receiving standard of care and are health outcomes comparable to the community?
- Within HIPAA guidelines, develop mechanisms in the VA system to identify and enroll veterans with ALS into the National ALS Disease Registry.
- Dept. of Veterans Affairs as a leader in funding and support of ALS research.