CDC PUBLIC HEALTH GRAND ROUNDS

National Amyotrophic Lateral Sclerosis (ALS) Registry Impact, Challenges, and Future Directions

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Accessible version: https://youtu.be/ov2KPuSW8kg
Overview of the National ALS Registry – Past, Present, Future

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Chief, Environmental Health and Surveillance Branch
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry (ATSDR)
Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, fatal neurological disease caused by the degeneration of motor neurons in the brain and spinal cord.

- Approximately 80% of patients die within 2–5 years of diagnosis.
- 10% are familial cases; 90% are sporadic cases.
- No known cause for sporadic cases.
- No cure.
Public Health Surveillance Barriers

- ALS is a non-notifiable disease

- Because of this, there is a lack of reliable incidence and prevalence estimates for the U.S. and by geographic area
Need for a National ALS Registry

- In October 2008, Congress passed the ALS Registry Act
  - Directed CDC/ATSDR to create a population-based ALS registry for the U.S.

- Registry objectives (as specified by the Act)
  - Describe incidence and prevalence of ALS
  - Describe the demographics of ALS patients
  - Examine risk factors for the disease

- Novel approach was needed to track ALS cases
- National ALS Registry was launched in October 2010
Overcoming Surveillance Challenges by Novel Methodology

**Algorithm:** ICD code, frequency of neurological visits, Rx drug usage

-National Databases*

-Apply Algorithm**

-National ALS Registry

-Web Portal Registration

-Validation Questions

-True ALS Patients

-Non ALS Patients

-True ALS Patient

-Potential ALS Patients

-Risk Factor Survey

* Medicare, Medicaid, Veterans Administration

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NATIONAL ALS REGISTRY

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Validation Questions

True ALS Patients
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Sharing ALS Surveillance Findings

- ATSDR publishes annual reports of our findings in *MMWR*

- Our third report for calendar year 2014 is anticipated to be published later this year
Registry Does More than Just Count ALS Cases: Specimen Collection and Research Funding

- Research
- National ALS Biorepository
- Epidemiology
- Partners
- Survey Data
- Research Notification Mechanism

NATIONAL ALS REGISTRY
Registry Does More than Just Count ALS Cases: Giving Patients Access to Clinical Trials

Research
National ALS Biorepository
Epidemiology
Partners
Survey Data
Research Notification Mechanism
NATIONAL ALS REGISTRY
Registry Partners

- Patients and caregivers
- National ALS patient organizations
  - ALS Association
  - Muscular Dystrophy Association
  - Les Turner ALS Foundation
- Healthcare providers
- Other federal agencies
- Research institutions (e.g., academia)
Impact of Registry

- First and only population-based ALS registry for the U.S. that is quantifying the epidemiology of the disease
- Used as a recruitment tool for domestic and international researchers
- Awarding funds for external research
- Providing epidemiologic data and biospecimens to scientists
- Building the evidence to better describe the ALS experience in the U.S.
The Known and Unknowns about ALS

Paul Mehta, MD

Principal Investigator, National ALS Registry
Environmental Health and Surveillance Branch
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry (ATSDR)
In 2013, 15,908 definite cases of ALS identified

- Prevalence rate of 5.0 cases per 100,000 persons

Epidemiology of ALS: Risk Factors

- ALS is found to be more common in
  - Whites
  - Persons aged 60–69 years

- **Lowest number of ALS patients among persons**
  - Ages 18–39 and >80 years

- **Males have a higher prevalence than females**

ALS and military service connection

- 50% greater risk of ALS than men who did not serve in the military
- Military personnel deployed to the Gulf Region during the Gulf War (1990–1991) had double the risk of those not deployed to the Gulf Region
- Possible link to environmental factors
- More research is needed and is ongoing
Epidemiology of ALS: Risk for Professional Athletes

ALS and football

- In one non-ALS registry study retired National Football League players were at four times greater risk of ALS.

- Need to confirm increased risk and better understand possible causes.

ALS Disease Trends

- National incidence stable
- Prevalence increasing slightly
  - Patients living longer with comprehensive, multidisciplinary care
  - Registry capturing more cases, better case ascertainment
- Additional years of data are needed to assess trends

CDC, unpublished data
Causes of ALS Remain Elusive

**Two type of ALS**

- **Sporadic (SALS):** 90% of cases
  - Environmentally linked
- **Familial (FALS):** 10% of cases
  - Genetically linked
  - Genetic counseling available

GWAS: Genome-wide association studies


GWAS: Genome-wide association studies
More than 60,000 surveys completed by more than 12,000 patients

Further exploration of etiology and risk factors

- Demographics, environmental and occupational exposures
ALS Registry Risk Factor Surveys

- 17 surveys, taken by patients who enroll via the online portal
- Shed light on ALS causes and factors that may either be protective or contribute to disease onset or progression
- Topics range from demographics to smoking, alcohol, disease progression, and environmental exposures such as pesticide use
- One survey allows patients to state what might have caused their ALS
- Survey data are also available to external researchers
Component of the National ALS Registry

- Launched in January 2017
- Expand ALS research in biomarkers, genetics, environmental exposures
- Sample collection will be geographically representative
National ALS Biorepository

In Home Collections
- Blood
- Urine
- Saliva

Post-Mortem Collections
- Bone
- Brain
- Spinal Cord
- CSF
- Muscle

Specimens for Research

Risk Factor Surveys from National ALS Registry

CSF: Cerebrospinal fluid
National ALS Biorepository

**In Home Collections**
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Specimens for Research

Risk Factor Surveys from National ALS Registry

CSF: Cerebrospinal fluid
Challenges for Research, Drug Development, and Patient Care

Edward J. Kasarskis, MD, PhD
Professor of Neurology
Cynthia Shaw Crispen Chair for ALS Research
University of Kentucky, Lexington
ALS Shares Some Clinical Characteristics with Other Neurodegenerative Diseases

- Alzheimer’s disease, Parkinson’s disease, and ALS are prototypical
  - ALS presents with insidious rather than acute onset of neurological dysfunction
  - Neurological deficits are concentrated in certain realms
    - Alzheimer’s disease: Cognitive and behavioral
    - Parkinson’s disease: Slowed movement (bradykinesia) and tremor
    - ALS: Weakness of most voluntary skeletal muscles

- ALS remains a clinical diagnosis
  - No definitive imaging biomarker
  - No definitive blood or cerebrospinal fluid biomarker
Clinical Characteristics of ALS

- **Onset of weakness in one bodily region**
- **Progression and spread from one region to involve other regions**
  - 80% limb onset
  - 20% “bulbar” onset
    - Difficulty speaking or swallowing
- **Relatively preserved function of some muscles and other neurologic functions**
  - Sensation
  - Sphincter control (i.e., bladder and bowel)
  - Eye movement
  - Awareness, cognition, and memory
Clinical Outcomes of ALS

- Uniformly fatal, typically due to respiratory failure
- Little effective treatment
  - Riluzole slows rate of progression and extends survival by at least 2–3 months

- Most ALS cases are sporadic without a family history of ALS
- However, 10% of cases are familial
  - More than 20 genes have been identified as causing familial ALS (fALS)
  - Typically, fALS patients have onset at a younger age
What Does “Weakness” Look Like in ALS?

- Images shown with permission
Weakness in ALS is Progressive

%FVC at Study Entry and 9-month Survival Probability

%FVC: Percent forced vital capacity
Degeneration and Death of Cortical and Spinal Motor Neurons is Source of Progressive Weakness in ALS

Preferential Upper and Lower Motor Neuron Loss

How Do We Diagnose ALS?
Challenges for Case Ascertainment in Epidemiology

(ALS remains a clinical diagnosis

- Coexistence of upper and lower motor neuron signs in a single bodily region
  - Upper motor neuron findings include overactive tendon reflexes, clonus, Hoffman and Babinski signs
  - Lower motor neuron findings include muscle atrophy, weakness, and fasciculation (i.e., muscle twitching)
- Verify normal functioning of other neurological systems, (e.g., sensation)

To some degree, ALS is a diagnosis of exclusion

Diagnosis of Exclusion:
Diagnosis reached by a process of elimination, if presence cannot be established from history, examination or testing
How Do We Diagnose ALS?
Challenges for Case Ascertainment in Epidemiology

- Diagnostic testing is essential to rule out so-called “ALS mimics”
  - These include multiple sclerosis, Parkinson’s disease, Alzheimer’s disease, and many others

- Testing may include
  - MRI of brain and spinal cord—structural causes of progressive weakness
  - EMG/NCV—evaluate for disease of muscle and/or nerve
  - Laboratory studies—endocrine, metabolic, immunologic, etc.

- All patients must have a second opinion from another neurologist
So, How Good Are Neurologists at Diagnosing ALS?

- **Actually, not bad at all**
  - Clinical diagnosis has 95% sensitivity compared to autopsy

- **Diagnostic standards**
  - Basic clinical principles: UMN/LMN findings
  - El Escorial criteria (1990; Arlie House, 1998)
  - Awagi criteria (2008)

- **Recent Scottish study**
  - 1,226 registry cases
  - 44 came to autopsy
    - 100% confirmation of ALS or motor neuron disease diagnosis

UMN: Upper motor neuron
LMN: Lower motor neuron
Despite these challenges, we are able to diagnose ALS or motor neuron disease with a fair degree of certainty

- This makes epidemiologic research possible

We have tools to measure progression of ALS

- These aid clinical drug development
Monitoring Progression of ALS

- **ALSFRS-R rating scale of function**
  - Self-report by patient, or even just the caregiver
  - Can be administered over the phone or on computer

- **Tests of pulmonary (ventilatory) function**
  - Percent forced vital capacity (%FVC)
  - Maximum inspiratory pressure (MIP)
  - Sniff nasal pressure (SNP)

- **Survival**
  - Without assisted ventilation

A spirometer measures lung function and is used to monitor changes in a person with ALS’s functional abilities.
Monitoring Progression of ALS

- **Functional measurements**
  - Gait speed
  - Timed up-and-go
  - Perdue pegboard

- **Quantitative muscle testing**
  - Manual muscle testing
  - Measures of isometric muscle power
Barriers to Progress

- By the time people become clinically impaired, the majority of vulnerable neurons have already degenerated and died
  - Estimates are perhaps 50%–70% of motor neurons are gone

- Large numbers of patients are required for clinical studies
  - Trials are labor-intensive and therefore costly; millions of dollars

- Barriers to progress for ALS patients and their families
  - Time: activities of daily living take longer, time away from work for family caregivers
  - Distance to tertiary care medical centers
  - Out-of-pocket expenses
Reasons for Optimism

- The ALS research community is expanding
- The ALS research community is creative, passionate, and committed
- The National ALS Registry stands as a prime example
- My prediction: ALS causes will be found and treatments will be developed
Living with ALS: A Patient’s Story

Ed Tessaro, BA

Person Living with ALS (PALS)
Making Connections to Make A Difference

- The ongoing struggle to encourage newly diagnosed patients to come forward, register, and take charge of their condition

Edward Rapp
Caterpillar

Daniel Doctoroff
Bloomberg News

Steve Ennis
Coca-Cola

Pete Frates
Ice Bucket Challenge

Bruce Thompson
Gold Key Resorts

Suzanne Malveau
CNN
Not All Costs Are Financial

Cost of living with ALS, fear of consequences, and the consequences of that fear

<table>
<thead>
<tr>
<th>Average Costs for the 20-month Diagnosis Seeking Period</th>
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</thead>
<tbody>
<tr>
<td>Professional fees for Physicians and therapists</td>
</tr>
<tr>
<td>Testing/procedure expenses including all out-patient care &amp; services</td>
</tr>
<tr>
<td>Inpatient hospitalization</td>
</tr>
<tr>
<td>Travel expenses</td>
</tr>
<tr>
<td>Treatments including enteral nutritional &amp; supplies</td>
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<tr>
<td>Other equipment &amp; supplies</td>
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<td>Medications</td>
</tr>
<tr>
<td>Medical records copies &amp; shipping</td>
</tr>
<tr>
<td>Caregiver salary</td>
</tr>
<tr>
<td><strong>Total Costs</strong></td>
</tr>
</tbody>
</table>

Increasing Openness of the Medical Community Would Help

- Openness of medical community, researchers, and investigators toward new patients and their families
Need to Lower Barriers for PALS and Increase Support

- The daunting patient process to determine eligibility for clinical trials, and to receive timely information
There is a great need to counsel patients in an affirmative way—to accept reality of the disease and turn it into their life-force

- Purposeful
- Selfless
- Self-determined
- Empowered
- Courageous
Practical and Relevant Resources

MDA
For Strength, Independence & Life

ALS Association
Create a world without ALS.
The Inherent Injustice and Necessity of Double-blind Trials

- ALS plateaus and reversals info—deserves more discussion
Expanding Access

- Right-to-try legislation
- Compassionate use
- Expanded access

Ted Harada
in memoriam
National Amyotrophic Lateral Sclerosis (ALS) Registry Impact, Challenges, and Future Directions