Kronkosky Charitable Foundation

Research Brief

Amyotrophic Lateral Sclerosis (ALS)

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Amyotrophic lateral sclerosis (ALS) is a progressive disease of the nervous system in which degeneration of nerves causes muscle weakness, paralysis, and ultimately, death. Quantifying the prevalence of ALS in the population is difficult because ALS is not a nationally notifiable disease. The federal Agency for Toxic Substances and Disease Registry (ATSDR) implemented a National ALS Registry in 2009 and launched a secure web portal in October 2010 through which individuals with a diagnosis of ALS can register and complete brief risk-factor surveys online. "The National ALS Registry is a congressionally mandated registry for persons in the U.S. with ALS. It is the only population-based registry in the U.S. that collects information to help scientists learn more about who gets ALS and its causes" (ATSDR, 2017a). Numbers of individuals diagnosed with ALS can also be gleaned from existing administrative databases including Medicare, Medicaid, the Veterans Health Administration, and the Veterans Benefits Administration (Centers for Disease Control and Prevention [CDC], 2016).

The Centers for Disease Control and Prevention (CDC) (2014) published the first surveillance report on the prevalence of ALS in the United States in July 2014 using data obtained from all five sources listed above. Texas state data was collected through a surveillance project funded by ATSDR "to gather reliable and timely data to describe the incidence and demographic characteristics of ALS and to assist ATSDR in evaluating the completeness of the Registry" (ATSDR, 2017b, p.1). As part of that project "all neurologists practicing in the state of Texas were asked if they diagnosed or provided care for ALS patients… Neurologists were asked to submit one-page case reports for ALS patients under the doctor's care who were alive at some point between January 1, 2009 and December 31, 2011" (ATSDR, 2017b, p.1). The following table shows results of both surveillance reports:

DEMOGRAPHIC CHARACTERISTICS OF ALS PATIENTS JANUARY 2009-DECEMBER 2011

	UNITED STATES		TEXAS	
	#	%	#	%
TOTAL REPORTED ALS	12,187		1,423	
GENDER				
Male	7,409	60.8	796	55.9
Female	4,740	38.9	627	44.1
Unknown	38	0.3		
RACE				
White	9,638	45.2	1,135	79.8
Black	798	0.9	93	6.5
Asian	NR*		21	1.5
Other	535	1.6	1	0.0
Unknown	1,216	52.3	173	12.2
ETHNICITY**				
Hispanic	25	1.3	213	15.0
Non-Hispanic	889	46.2	1,053	74.0
Unknown	1,012	52.5	157	11.0
AGE				
Under 40	506	4.2	82	5.7
40-49	1,356	11.1	201	14.1
50-59	2,590	21.3	351	24.7
60-69	3,795	31.1	426	29.9
70-79	2,895	23.8	276	19.4
80+	952	7.8	76	5.3
Unknown	93	0.8	11	0.8

*Not reported in CDC surveillance
**Ethnicity reported for web portal only, not available in the national databases

(CDC, 2014; ATSDR, 2017b)

WHAT IS ALS?

"Amyotrophic lateral sclerosis, is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. A-myo-trophic comes from the Greek language. "A" means no. "Myo" refers to muscle, and "Trophic" means nourishment – "No muscle nourishment." When a muscle has no nourishment, it "atrophies" or wastes away. "Lateral" identifies the areas in a person's spinal cord where portions of the nerve cells that signal and control the muscles are located. As this area degenerates it leads to scarring or hardening ("sclerosis") in the region" (ALS Association, 2017c). ALS is also commonly referred to as Lou Gehrig's disease (after the famous baseball player who died from it), Charcot's disease (after the physician who first identified it in 1865) and motor neuron disease (which describes the disease mechanism) (ALS Therapy Development Institute [ALSTDI], n.d.b).

ALS affects only the nerves involved in voluntary muscle movement (motor neurons). Other nervous system functions such as cognition and the senses (hearing, seeing, smelling, tasting, and touch) are not affected. "Because people with ALS usually retain their ability to perform higher mental processes such as reasoning, remembering, understanding, and problem solving, they are aware of their progressive loss of function and may become anxious and depressed" (National Institute of Neurological Disorders and Stroke [NINDS], n.d.).

In general, ALS is categorized as either *sporadic* (occurs at random with no identifiable risk factors) or *familial* (inherited genetic disease). 90-95% of all ALS cases are considered to be sporadic (NINDS, n.d.). All forms of ALS are progressive – neurodegeneration continues inexorably. There is evidence to suggest that the rate of decline varies from person to person but is constant for each individual (Turner and Swash, 2015).

MEDICAL CLASSIFICATION

There are five distinct classifications for ALS used by physicians:

- *Classical ALS* affects approximately two thirds of PALS and is "characterized by a deterioration of upper and lower motor neurons (nerve cells)"
- *Primary Lateral Sclerosis (PLS)* is the rarest form of ALS where "the upper motor neurons (nerve cells) deteriorate. If the lower motor neurons are not affected within two years, the disease usually remains a pure upper motor neuron disease"
- *Progressive Bulbar Palsy (PBP)* affects approximately 25% of PALS and "starts with difficulties in speaking, chewing and swallowing due to lower motor neuron (nerve cell) deterioration"
- *Progressive Muscular Atrophy (PMA)* is characterized by deterioration of the lower motor neurons. "If the upper motor neurons are unaffected within two years, the disease usually remains a pure lower motor neuron disease"
- *Familial ALS* "affects more than one member of the same family and that's due to a known gene mutation. This type of ALS accounts for a very small number of people with ALS in the United States (between 5 and 10 percent)"

(Johns Hopkins Medicine, n.d.)

RISK FACTORS

A large variety of potential risk factors for developing ALS have been studied with no clear causes coming to light. There is still little known about why the disease manifests in any particular individual. Even in the small number of genetically linked forms, mutations have been identified on over a dozen different genes but not one is found in all PALS. Aside from being white, male, and between 40-70 years old (average age of 55 at diagnosis), the only real identified risk at this time is military service. Military veterans are approximately twice as likely to develop ALS (ALS Association, 2017d; Turner & Swash, 2015). The evidence was so strong that, "In July 2008, in response to the evidence, Secretary of Veterans Affairs Dr. James B. Peake announced that ALS is to be considered a presumptively compensable illness for all veterans with 90 days or more of continuously active service in the military" (ALSTDI, n.d.a).

Diagnosis

There is no definitive test to diagnose ALS. A physician reviews the patient's medical history and symptoms and conducts a series of tests to rule out other neurological diseases which may be treatable. The process can be lengthy (up to 12-14 months) because a primary sign of ALS is the progression of the signs and symptoms through a series of neurological tests over time (ALSTDI, n.d.b). The current requirement calls for "repetition of clinical and electrophysiological examinations at least six months apart to ascertain evidence of progression" (ALS Association, 2016b).

Some of the tests used to rule out other neurological diseases include:

- *Electromyography (EMG)* which measures the ability of muscles to respond to electrical stimuli (contract)
- *Nerve Conduction Study (NCS)* which tests the ability of the nerves to provide sufficient stimuli to cause the muscles to contract
- *Magnetic Resonance Imaging (MRI)* of the brain and spinal cord, while normal in PALS, may rule out other conditions such as tumors, cysts, herniated disks, etc. which may mimic ALS symptoms
- *Routine Laboratory tests* including blood and urine samples and thyroid function tests

(NINDS, n.d.)

There are three types of ALS diagnoses, the distinctions of which are primarily used for inclusion in clinical trials:

- *Definite ALS* is diagnosed when the loss of both upper and lower motor neurons is present in two or more regions of the body
- *Probable ALS* is also a diagnosis requiring the loss of both upper and lower motor neurons in two or more regions of the body (the difference between Definite ALS and Probable ALS is one of degree)
- *Possible ALS* is diagnosed if the loss of both upper and lower motor neurons is detected in only one region of the body

(ALSTDI, n.d.a; Calvo, et al., 2014)

Most patients who received an initial diagnosis of Probable or Possible ALS will ultimately progress to Definite ALS. The average length of time that PALS survive after diagnosis is 30 months with most people living between two to five years. Most individuals die of respiratory failure and/or other complications for the disease (ALS Association, 2017d; ALSTDI, n.d.a). "ALS has the shortest median survival among neurodegenerative disorders" (Turner and Swash, 2015, p.671).

Symptoms

Onset of symptoms for ALS vary per individual and "it has been estimated that one-third of large motor neurons must be lost before there is visible atrophy" (Turner and Swash, 2015, p.668). Typical signs and symptoms that a person may experience include:

- Trouble grasping or lifting objects
- Change in vocal pitch when speaking
- Tripping
- Dropping things
- Abnormal fatigue of the arms and/or legs
- Slurred speech
- Difficulty swallowing
- Weakness in hands, legs, feet, or ankles
- Muscle cramps and twitches
- Uncontrollable periods of laughing or crying

(ALSTDI, n.d.b; ALS Association, 2016c)

Treatment

There is no cure for ALS, the disease is always fatal. Treatment revolves around extending quality of life for the individual:

- Medications can help relieve some symptoms
  - Ease muscle cramps
  - Reduce fatigue
  - Reduce excess saliva and phlegm
  - Control spasticity
  - Fight depression
- Physical therapy can strengthen unaffected muscles and cardiovascular health
- Occupational therapy to use mobility devices such as canes, walkers, and wheelchairs
- Speech therapy to assist communication
- Nutritional support including the use of feeding tubes to reduce the risk of choking

- Breathing devices to aid breathing during sleep
- Mechanical ventilation

(NINDS, n.d.)

There are currently two FDA approved drug treatments for ALS:

- Riluzole (*Rilutek*) prolongs survival by a few months (usually a three-month life extension) but does not reverse the damage already done to motor neuron
- Edaravone (*Radicava*) is the newest treatment available and has been shown to slow the decline of daily functioning

(ALSTDI, n.d.a; NINDS, n.d.)

ALS patients often times look for alternative or off-label treatments (AOTs). Because information about these treatments is often found through the internet, and the information is not always accurate, the North American ALS Research Group developed a process to scientifically review AOTs (The ALSUntangled Group, 2015). To date, 41 AOTs have been evaluated by the review team and are available on the ALSUntangled (n.d.) website. PALS can request that a treatment or product be evaluated simply by sending a tweet to #ALSUntangled.

The cost associated with ALS is high. It is estimated that the annual cost per patient is approximately $69,475 (in 2015 U.S. dollars) with an annual economic burden in the United States of $276-472 million (Gladman and Zinman, 2015).

Multidisciplinary Centers

Multidisciplinary centers provide all of the supportive care needed by PALS in one location. These consist of "teams of health care professionals such as physicians; pharmacists; physical, occupational, and speech therapists; nutritionists; and social workers and home care and hospice nurses. Working with patients and caregivers, these teams can design an individualized plan of medical and physical therapy and provide special equipment aimed at keeping patients as mobile and comfortable as possible" (NINDS, 2016).

The ALS Association has a program that certifies multidisciplinary clinics based on the level of care provided. "Certifications are based on established requirements of the program, professionals' skill sets, people living with ALS served, active involvement in ALS-related research, relationships with local Chapters, and access to care" (ALS Association, 2017a). It lists a variety of treatment centers based on the level of services provided:

- *ALS Association Certified Treatment Centers of Excellence* meet all clinical care and treatment standards, provide evidence-based, multidisciplinary ALS care and services in a supportive atmosphere with an emphasis on hope and quality of life, participate in ALS-related research, and complete a comprehensive site review. There are three certified clinics listed in Texas: Baylor College of Medicine in Houston, the University of Texas Health Science Center-San Antonio, and the Houston Methodist ALS Clinic
- *ALS Association Recognized Treatment Centers* provide the same level of care as the certified centers but do not offer research or clinical trials.

(ALS Association, 2017a)

Additionally, there are many ALS clinics and private practitioners who work with ALS patients that, while they have not undergone the ALS Association's certification process, are nonetheless providing quality care. Many of these often work through university systems and nonprofit healthcare systems as well as with local ALS Chapters. Examples include: VA Clinics across the country and Baylor Scott & White Health Emory Bellard ALS Clinic in Austin, Texas. The ALS Association website lists ALS clinics (certified, recognized, and non-affiliated) in each state (ALS Association, 2017a).

Caregivers

Caring for PALS generally falls to family members. As the disease progresses, caregiving can become a 24/7 commitment. "Caregiving can include personal care, assistance with mobility in the home, transportation,

housework, and grocery shopping, along with looking after other family members' needs. Caregivers are often employed outside the home and may be the primary source of household income which adds even more demands, responsibilities and stress" (ALS Association, 2014). Family caregiving statistics include:

- Over 65 million individuals provide care for a chronically ill, disabled or aged family member during any given year
- It is estimated that 80% of home care services are provided by family caregivers
- Approximately 66% of caregivers are women
- The value of services provided by family caregivers is estimated to be $375 billion each year

(ALS Association, 2014)

Caregivers are subject to burn-out, fatigue, and stress-related illness. It is important that they have support systems in place to assist them in maintaining their own health as well as caring for their loved one. Some resources available to caregivers include:

- Assistive technology
  - Personal care: adaptive clothing, sliding transfer systems, portable showers
  - Alert and safety systems: pagers or alarms and systems such as "nanny cams" allow for remote monitoring
  - Home modifications: automation systems for opening doors, turning on electronic devices such as TVs or radios
  - Portable ramps: allow for wheelchair access for thresholds or stairs without permanent modifications
- Support Groups: connecting with others in the same situation
- Respite Care
  - In home: depending on the level of care needed, either a trained professional from a home health agency or a volunteer can come to the home for a few hours or a day to give the caregiver a break
  - Out-of-home: the loved one is taken to a facility with trained staff on-site for a period of time

(ALS Association, 2014)

Ongoing Research

Numerous research studies are investigating several aspects of ALS:

- Studies to determine the mechanisms of the disease process – what triggers the motor neurons to degenerate
- Innovative cell culture systems to induce skin or blood cells to become stem cells which can then become motor neurons and other cell types that may be involved in the disease
- Development of biomarkers to serve as diagnostic tools to not only detect the disease but serve as targets for therapy
- Potential therapies such as drug compounds, gene therapy, and antibody and cell-based therapies for more effective treatment

(NINDS, n.d.)

Clinical trials are used to determine if a potential new test or treatment is safe and effective. The clinicaltrials.gov website (n.d.) lists 389 clinical trials for ALS-related research studies. PALS enrolled in the National ALS Registry may also participate in the ALS Biorepository by allowing collection of various blood/tissue samples which will then be available to researchers for use in ALS studies (ATSDR, 2017a).

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