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ALS

Living Inside a Dying Body

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Developed for *The Voice,* this article aims to raise awareness and understanding of ALS.

Amyotrophic Lateral Sclerosis (ALS) is an aggressive, fatal neurodegenerative disease that claims thousands of lives every year. This disease knows no boundaries—it affects people of all backgrounds, creeds, and ethnicities. To this day there is no known cure or effective treatment, leaving its victims to endure the two-to-five year life expectancy their diagnosis imparts trapped inside of a dying body. Current research efforts are aimed at understanding the development and progression of the disease in hopes of a future treatment, but the exact causes of ALS still elude researchers. More research and funding are needed, highlighting the necessity for an increased awareness of this small, but deadly killer.

Readability Statistics

Counts		Averages		Readability	
Words	1668	Sentences per Paragraph	6.5	Passive Sentences	8%
Characters	8968	Words per Sentence	20.9	Flesch Reading Ease	38.4
Paragraphs	24	Characters per Word	5.2	Flesch-Kincaid Grade Level	12.0
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Living Inside a Dying Body

When Jonathan Blais called home to inform his parents that he had Amyotrophic Lateral Sclerosis (ALS), they were overwhelmed with surprise and fear. Blais, a triathlete and special education teacher, received his diagnosis at 33, and was essentially given a death sentence. According to estimates, physicians diagnose 5,000 people with ALS in the United States each year, with 350,000 currently living with the disease worldwide. Approximately 80% of all diagnosed patients die within two to five years, and all eventually succumb to the disease.[2]

According to Jon's father, "We always expected that sometime there might be a phone call, that Jon has had an accident… We were never expecting a phone call from our son to tell us that, 'You know, I think I've got ALS—Lou Gehrig's disease.' After his diagnosis I said to him, 'Jon, you're coming home to live, not die.'"[3]

ALS progresses swiftly and steadily, and no cure or treatment yet exists that can stop or reverse the course of the disease. Though thousands of individuals are diagnosed with this fatally progressive disease each year, there remains a significant lack of awareness about the condition.

What is ALS?

ALS, more commonly known as Lou Gehrig's disease in the United States, is a fatal neuromuscular disorder that affects the body's motor neurons. Motor neurons are specific cells within the central nervous system that conduct messages between the brain, spinal cord, and skeletal muscles. Upper motor neurons (UMNs) first send messages from the brain to the spinal cord. From here, lower motor neurons (LMNs) send their long cellular extensions to muscles throughout the body. The communication between these cells allows the motor command center of the brain to coordinate complex, voluntary movements like walking, speaking, chewing, and breathing.[4]

When motor neurons begin to degenerate, the symptoms of ALS arise. Early symptoms are often slight and manifest as muscle weakness. Consequently, both patients and physicians often overlook early signs. When motor neurons degenerate, they cannot communicate with skeletal muscles, and muscle

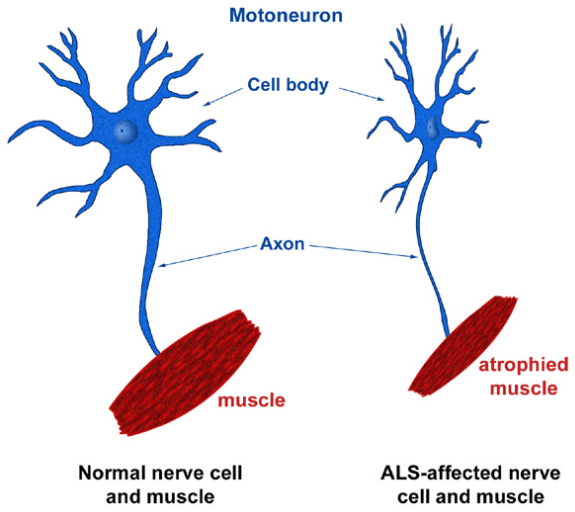

Figure 1: ALS causes nerve cells and muscles to waste away *http://len.epfl.ch/webdav/site/len/shared/import/migration/ALS1.jpg*

paralysis ensues (Figure 1). If the early degeneration primarily affects UMNs, patients often experience weakness, fatigue, and stiffness; if mostly LMNs are affected, common symptoms include weakness, muscle wasting, muscle twitches, and muscle cramps. All of these

symptoms are somewhat broad and commonplace, and because there is no biomarker available to test, patients must rely on clinical studies to receive a diagnosis.[4]

This makes early diagnoses of ALS particularly difficult. In order to receive a clinical diagnosis, physicians must check that patients' symptoms conform to the El Escorial Criteria, a set of five standards established by the World Federation of Neurology in 1990. These criteria include degeneration of both UMNs and LMNs, and the spread of degeneration to other regions of the body. In addition, there cannot be any evidence of other diseases that could explain the degeneration.[5] Waiting for all of these criteria to exhibit can be problematic, because once ALS attacks, it progresses extremely quickly. By the time most patients receive a clinical diagnosis, many already have a 50% degeneration of their LMNs.[6] This means less time for possible therapeutic treatments, and less time to live within an already short, two-to-five year life expectancy.

Paralysis increases as ALS progresses, yet patients' senses and mental capacity generally remain completely intact. As a consequence, individuals diagnosed with ALS are essentially living within a dying body, waiting and watching as their physical being succumbs to the disease. Patients eventually lose the ability to swallow, speak, chew, and breathe without assistance, and eventually die from respiratory failure (Figure 2).

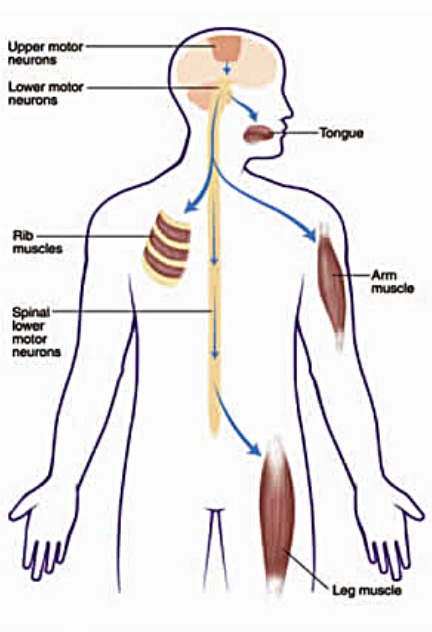

Figure 2: Degeneration of neurons affects arm, leg, rib, and tongue muscles. *http://media.jaapa.com/images/2009/05/15/J0706als_f1_54354_54357.jpg*

Understanding ALS: Two Forms, One Known Link

ALS affects individuals of all backgrounds, and typically develops in adults between 40 and 70 years of age.[2] In 90-95% of all cases, the disease develops spontaneously. Physicians call these spontaneous cases Sporadic ALS (SALS), and they largely remain a mystery. About 5-10% of all individuals diagnosed with ALS have at least one previously affected family member; these cases are classified as Familial ALS (FALS). Since the prevalence of SALS is so much higher than FALS, scientists originally thought that ALS had no genetic component. As genetic technology and statistical tools became more advanced, however, the role that genetics plays in the disease became clearer.[4]

In 1993, Daniel Rosen of Brandeis University discovered a genetic mutation that affects 20% of all FALS patients. This mutation affects the antioxidant enzyme called copper/zinc superoxide dismutase (SOD1), which plays an important role in protecting the cell from destructive free radicals called superoxides.[7] This was a landmark discovery in ALS research, because it spearheaded the use of molecular techniques and information to understand the causes and possible treatments of the disease. Since Rosen's discovery, researchers have uncovered over 100 different mutations throughout the SOD1 gene, but it is still unknown how these specific changes cause the progressive death of motor neurons that classifies ALS. Moreover, since SOD1 mutations only play a role in 20% of FALS cases, or one percent of all ALS diagnoses, the breach in knowledge about SALS remains expansive.

Research and Treatment Difficulties

Over the past fifteen years, researchers have focused intensely on trying to understand the molecular and cellular mechanisms that cause ALS onset and progression. Most research is conducted on mice models that have been

genetically modified to develop an ALS-like disease. The problem with such models, however, is that therapeutic interventions based on animal models do not always translate well into effective human treatments.[7]

Furthermore, ALS is a multietiological disease–many genes are involved in causing both sporadic and familial forms of ALS. While scientists believe that several genes like SOD1 play a role in FALS cases, they do not fully understand the mechanisms. On the other hand, scientists believe that Sporadic ALS develops as a consequence of various genetic and environmental interactions. Without knowing exactly what these interactions are, however, it is impossible to develop effective treatments.[1]

Due to the rapid progression of ALS, the typically late diagnosis, and the poorly understood mechanistic causes, ALS remains an extremely difficult disease to treat. To date, there is no cure for ALS, and the standard course of treatment calls for administering the drug Riluzole to patients. Of the many drugs that yielded positive results in animal studies, Riluzole is the only one that has a positive impact on either prolonging survival or improving the life quality of ALS patients.[8] As such, Riluzole is the only drug approved for the treatment of ALS in Europe, the United States, and Australia.

Despite the accepted use of Riluzole for ALS treatment, it only modestly slows the disease progression. In fact, Robert Miller of the Forbes Norris ALS Research Center found that Riluzole only prolongs the average ALS patient's life expectancy by two to three months.[9] While the drug may lengthen life expectancy somewhat, it commonly results in nausea and fatigue, and costs more than $11,000 a year, which raises the question of whether the benefits of the treatment are justified by the exorbitant costs.[10]

Considering that Riluzole is a less-than-optimal option for the management of ALS, there is a great deal of research being conducted on alternative treatments. One promising area for inherited FALS cases is gene silencing. Gene silencing techniques turn down or turn off the expression of certain genes, which causes the body to make fewer copies of mutant, disease-causing proteins. This method has proved successful in mouse models, which holds hope for future clinical applications[11]

As the general understanding of ALS disease-causing mechanisms has increased over the past thirty years, more clinical trials have become available (Figure 3).

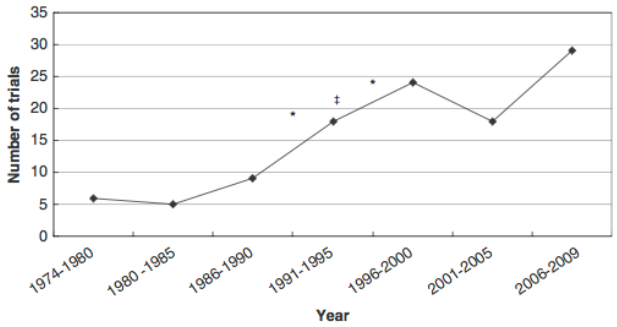

Figure 3: Number of Phase II or III clinical trials in ALS[1]

There are currently twenty-five active clinical trials, many of which are particularly exciting. In January of 2010, for example, the FDA granted approval to the biotechnology company Neuralstem, Inc. to provide stem cell injections into the spinal cords of ALS patients. Dr. Eva Feldman, the University of Michigan neurologist overseeing the study, hopes that the stem cells protect the still-functioning neurons in the patients' nervous systems.[12] The success of this trial is yet to be determined.

Likewise, The FDA recently reapproved a previously suspended drug called Arimoclomol for a clinical trial. Arimoclomol improved survival rate and muscle function in ALS mouse models, and functions by increasing the production of heat shock proteins, which help gather up toxic, misfolded proteins in damaged cells.[1] Clinical trials like these give hope for future treatment options, but underscore the need for additional research, funding, and attention for ALS.

A Call to Arms

Despite the current research and clinical models aimed at rectifying the lack of treatment

options for ALS patients, Riluzole remains the only approved option. ALS is a story without an answer—a small, but devastating disease that is often pushed to the side and forgotten about. For the thousands of individuals diagnosed each year, ALS is a death sentence, but it often inspires them to do great things in the little time they have left.

Six months after his diagnosis, Jon Blais participated in the Ironman World Championships in Kona, Hawaii, a grueling 140.6-mile course that incorporates swimming, biking, and running. Though the disease had already rendered one of his arms mostly useless, he declared that he would finish the race, even if he had to roll himself across the finish. Jon completed the Ironman, crossing through the finish chute in a now symbolic log roll. Despite completing the event, Jon's body continued to be ravaged by ALS. The next year at Kona, Jon watched on as a spectator, his body constrained to a wheelchair; the following year he was gone.

The speed and horror with which ALS claims its victims leaves many individuals forgotten after death. More than anything, ALS needs a face for people to identify with as a means of raising awareness. For many individuals, Jon Blais is that face. This is clear in the log rolls many triathletes perform across the finish line of races, sounding the cry of Blais to recognize this horrific disease.

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Kyle Ryan *is a senior Neurobiology, Physiology, and Behavior major at UC Davis. After he graduates, he plans to pursue a career in medicine. Outside of the classroom, Kyle likes to practice his Spanish, cook, discover new music, and train for triathlons. Watch for him log rolling across triathlon finish lines in the future.*