



## Review Article

# AMYOTROPHIC LATERAL SCLEROSIS : A REVIEW

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## ABSTRACT

Amyotrophic lateral sclerosis (ALS) also called Lou Gehrig's disease is a rapidly progressive, invariably fatal neurological disease that attacks the nerve cells (neurons) that responsible for controlling voluntary muscles. several known ALS genes were found to be associated and TBK1 (the gene encoding TANK binding kinase) was identified as an ALS gene. In the United States, more than 5,600 are diagnosed every year, and up to 30,000 Americans are currently affected. ALS is responsible for two deaths per 100,000 people per year. Smoking, Lead exposure & Heredity are the major factor for ALS. No cure has yet been found for ALS. However, the Food and Drug Administration (FDA) approved the first drug i.e. riluzole (Rilutek)—in 1995. Riluzole is believed to reduce damage to motor neurons by decreasing the release of glutamate. However, new medications or combinations of drugs would be beneficial for cure or prevention of disease.

**KEY WORDS:** Amyotrophic lateral sclerosis, TBK1, Lead exposure, Riluzole

## INTRODUCTION

Amyotrophic lateral sclerosis or A.L.S. , is a nervous system (neurological) disease that causes muscle weakness and impacts physical function. ALS is often called Lou Gehrig's disease, after the famous baseball player who was diagnosed with it. ALS is a type of motor neuron disease that causes nerve cells to gradually break down and die. In the United States, ALS is sometimes called motor neuron disease. In most cases, doctors don't know why ALS occurs.

A small number of cases are inherited. ALS often begins with muscle twitching and weakness in an arm or leg, or sometimes with slurring of speech. Eventually, ALS can affect your ability to control the muscles needed to move, speak, eat and breathe. ALS can't be cured and eventually leads to death. Amyotrophic lateral sclerosis (ALS), sometimes called Lou Gehrig's disease, is a rapidly progressive, invariably fatal neurological disease that attacks the nerve cells (neurons) responsible for controlling voluntary muscles (muscle action we are able to control, such as those in the arms, legs, and face).

The disease belongs to a group of disorders known as motor neuron diseases, which are characterized by the gradual degeneration and death of motor neurons. Motor neurons are nerve cells located in the brain, brain stem, and spinal cord that serve as controlling units and vital communication links between the nervous system and the voluntary muscles of the body. Messages from motor neurons in the brain (called upper motor neurons) are transmitted to motor neurons in the spinal cord (called lower motor neurons) and from them to particular muscles. In ALS, both the upper motor neurons and the lower motor neurons degenerate or die, and stop sending messages to muscles.

ALS causes weakness with a wide range of disabilities. Eventually, all muscles under voluntary control are affected, and individuals lose their strength and the ability to move their arms, legs, and body. When muscles in the diaphragm and chest wall fail, people lose the ability to breathe without ventilatory support. Most people with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. However, about 10 percent of those with ALS survive for 10 or more years.

Although the disease usually does not impair a person's mind or intelligence, several recent studies suggest that some persons with ALS may have depression or alterations in cognitive functions involving decision-making and memory. ALS does not affect a person's ability to see, smell, taste, hear, or recognize touch. Patients usually maintain control of eye muscles and bladder and bowel functions, although in the late stages of the disease most individuals will need help getting to and from the bathroom. "Motor neuron disease" redirects here. For the broader group of diseases, see Motor neuron disease.

## RESEARCH

A number of clinical trials are underway globally for ALS; a comprehensive listing of trials in the US can be found at ClinicalTrials.gov. The world's largest genetic study, called project Min E, initiated by two people with ALS is going on currently. It is a crowd funded research project with many countries involved to discover more genes. A phase-II trial on tirasemtiv has been completed with a follow-on phase-IIb study in progress under the name "BENEFIT-ALS". Results of the first study are available here. unreliable medical source, verification needed The current trial is an international, placebo-controlled, multiple-center study on 680 participants. This makes it one of the largest studies to date. A phase-II trial on ozanezumab is in progress. It is a large multiple-site international research project sponsored by GlaxoSmithKline. A phase-II clinical trial is being conducted by Brain Storm Cell Therapeutics at the Hadassah Medical Center in Israel and interim results "demonstrated a tendency toward stabilization in some parameters in the ALS Functional Rating Scale." People in the trial have bone marrow stem cells removed and differentiated in a clean room into cells that express neuro tropic factors.

The National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health, is the Federal Government's leading supporter of biomedical research on ALS.

Scientists are seeking to understand the mechanisms that selectively trigger motor neurons to degenerate in ALS, and to find effective approaches to halt the processes leading to cell death. This work includes studies in animals to identify the molecular means by which ALS-causing gene mutations lead to the destruction of neurons. To this end, scientists have developed models of ALS in a variety of animal species, including fruit flies, zebra fish, and rodents. Initially, these genetically modified animal models focused on mutations in the SOD1 gene but more recently, models harboring other ALS-causing mutations also have been developed.

Increasing evidence also suggests that various types of glial support cells and inflammation cells of the nervous system play an important role in the disease.

2 Recent research has shown that the defect in the C9orf72 gene found in familial ALS is also present in a small percentage of sporadic ALS cases.

Further, there is evidence that mutant SOD1 is present in spinal cord tissue in some sporadic cases of ALS. In the

case of ALS, researchers have been able to convert pluripotent stem cells derived from skin into becoming motor neurons and other cell types that may be involved in the disease.

## CLASSIFICATION

Three classifications of ALS have been described:

- **Sporadic** –
  - The most common form of ALS in the United States - 90 to 95% of all cases.
- **Familial** –
  - Occurring more than once in a family lineage (genetic dominant inheritance) accounts for a very small number of cases in the United States - 5 to 10% of all cases.
- **Guamanian** –
  - An extremely high incidence of ALS was observed in Guam and the Trust Territories of the Pacific in the 1950's. The most common form of ALS in the United States is "sporadic" ALS. It may affect anyone, anywhere. "Familial" ALS (FALS) means the disease is inherited. Only about 5 to 10% of all ALS patients appear to have genetic or inherited form of ALS. In those families, there is a 50% chance each offspring will inherit the gene mutation and may develop the disease.
- **Familial ALS:**
  - Most of the time ALS is not inherited. In about 90% of cases, the person is the only member of the family with the disease. These cases are called "sporadic ALS". The cause of sporadic ALS is not well understood, but may be due to a combination of environmental and genetic risk factors. About 10% of cases are considered "familial ALS" (FALS). In these cases, more than one person in the family has ALS and sometimes family members have frontotemporal dementia as well. People with FALS often start having symptoms at earlier ages than in sporadic ALS.
- **FALS is most often autosomal dominant.**
  - This means a parent who has a genetic change (or mutation) that causes ALS has a 50% chance of passing that mutation to each of his or her children. Both men and women are equally likely to inherit the genetic mutation.

## SIGN & SYMPTOMS

Tests to confirm ALS or look for other causes of your symptoms include:

- Muscle twitching
- Trouble using your hands and fingers to do tasks.
- Problems with speaking, swallowing, eating,

walking, and breathing.

- Problems with memory, thinking, and changes in personality. But these are not common.
- ALS doesn't cause numbness, tingling, or loss of feeling.
- Electromyogram (EMG):-which helps measure how well nerves and muscles work.
- Magnetic resonance imaging (MRI):- which can show problems or injury in the brain.

Nerve conduction studies to test nerve function. As the muscles in the throat and chest weaken, swallowing, coughing, and breathing problems tend to get worse. Pneumonia, pulmonary embolism, lung failure, and heart failure are the most common causes of death. The first sign of ALS is often weakness in one leg, one hand, the face, or the tongue. The weakness slowly spreads to both arms and both legs.

This happens because as the motor neurons slowly die, they stop sending signals to the muscles. So the muscles don't have anything telling them to move. Over time, with no signals from the motor neurons telling the muscles to move, the muscles get weaker and smaller. The disorder causes muscle weakness and atrophy throughout the body due to the degeneration of the upper and lower motor neurons. Individuals affected by the disorder may ultimately lose the ability to initiate and control all voluntary movement, although bladder and bowel function and the muscles responsible for eye movement are usually spared until the final stages of the disorder.

### INITIAL SYMPTOMS

Early signs and symptoms of ALS include:

- Difficulty walking, tripping or difficulty doing your normal daily activities
- Weakness in your leg, feet or ankles
- Hand weakness or clumsiness
- Slurring of speech or trouble swallowing
- Muscle cramps and twitching in your arms, shoulders and tongue
- Difficulty holding your head up or keeping a good posture

### REASONS

In ALS, the nerve cells that control the movement of your muscles gradually die, so your muscles progressively weaken and begin to waste away. Researchers are studying several possible causes of ALS, including:

- Gene mutation:- Various genetic mutations can lead to inherited ALS, which appears nearly identical to the non inherited form.
- Chemical imbalance:- People with ALS generally have higher than normal levels of glutamate, a chemical messenger in the brain, around the nerve cells in their spinal fluid. Too much glutamate is known to be toxic to some nerve cells.
- Disorganized immune response:- Sometimes a person's immune system begins attacking some of his or her body's own normal cells, which may lead to the death of nerve cells.

Protein mishandling:- Mishandled proteins within the nerve cells may lead to a gradual accumulation of abnormal forms of these proteins in the cells.

Heredity: Five to 10 percent of the people with ALS inherited it (familial ALS). In most people with familial ALS, their children have a 50-50 chance of developing the disease.

- Age: ALS most commonly occurs in people between the ages of 40 and 60.
- Sex: Before the age of 65, slightly more men than women develop ALS. This sex difference disappears after age 70.
- Smoking: Smoking cigarettes appears to increase a person's risk of ALS to almost twice that of a non smoker. The more years spent smoking, the greater the risk. However, quitting smoking can eventually lower the increased risk.
- Lead exposure: Some evidence suggests that exposure to lead in the workplace may be associated with the development of ALS.
- Military service: Recent studies indicate that people who have served in the military are at higher risk of ALS. Exactly what about military service may trigger the development of ALS is uncertain, but it may include exposure to certain metals or chemicals, traumatic injuries, viral infections and intense exertion.

### DIAGNOSIS

MRI (axial FLAIR) demonstrates increased T2 signal within the posterior part of the internal capsule, consistent with the diagnosis of ALS. No test can provide a definite diagnosis of ALS, although the presence of upper and lower motor neuron signs in a single limb is strongly suggestive.

Instead, the diagnosis of ALS is primarily based on the symptoms and signs the physician observes in the person and a series of tests to rule out other diseases.

Physicians obtain the person's full medical history and usually conduct a neurologic examination at regular intervals to assess whether symptoms such as muscle weakness, atrophy of muscles, hyperreflexia, and spasticity are worsening. Because symptoms of ALS can be similar to those of a wide variety of other, more treatable diseases or disorders, appropriate tests must be conducted to exclude the possibility of other conditions.

One of these tests is electromyography (EMG), a special recording technique that detects electrical activity in muscles. Certain EMG findings can support the diagnosis of ALS. Another common test measures nerve conduction velocity (NCV). Specific abnormalities in the NCV results may suggest, for example, that the patient has a form of peripheral neuropathy (damage to peripheral nerves) or myopathy (muscle disease) rather than ALS. While a magnetic resonance imaging (MRI) is often normal in people with ALS, they can reveal evidence of other problems that may be causing the symptoms, such as a

spinal cord tumor, multiple sclerosis, a herniated disk in the neck, syringomyelia, or cervical spondylosis. Based on the person's symptoms and findings from the examination and from these tests, the physician may order tests on blood and urine samples to eliminate the possibility of other diseases, as well as routine laboratory tests.

In some cases, for example, if a physician suspects the person may have a myopathy rather than ALS, a muscle biopsy may be performed. Viral infectious diseases such as human immunodeficiency virus (HIV), human T-cell leukaemia virus (HTLV), Lyme disease, syphilis and tick-borne encephalitis can in some cases cause ALS-like symptoms.

Neurological disorders such as multiple sclerosis, post-polio syndrome, multifocal motor neuropathy, CIDP, spinal muscular atrophy, and spinal and bulbar muscular atrophy can also mimic certain aspects of the disease and should be considered.

## **THERAPY**

Physical therapy plays a large role in rehabilitation for individuals with ALS. Specifically, physical and occupational therapists can set goals and promote benefits for individuals with ALS by delaying loss of strength, maintaining endurance, limiting pain, preventing complications, and promoting functional independence. Occupational therapy and special equipment such as assistive technology can also enhance patients' independence and safety throughout the course of ALS. Gentle, low-impact aerobic exercise such as performing activities of daily living, walking, swimming, and stationary bicycling can strengthen unaffected muscles, improve cardiovascular health, and help patients fight fatigue and depression.

Range of motion and stretching exercises can help prevent painful spasticity and shortening (contracture) of muscles. Physical and occupational therapists can recommend exercises that provide these benefits without overworking muscles. They can suggest devices such as ramps, braces, walkers, bathroom equipment (shower chairs, toilet risers, etc.), and wheelchairs that help patients remain mobile. Occupational therapists can provide or recommend equipment and adaptations to enable people to retain as much safety and independence in activities of daily living as possible. ALS patients who have difficulty speaking may benefit from working with a speech-language pathologist.

These health professionals can teach patients adaptive strategies such as techniques to help them speak louder and more clearly. As ALS progresses, speech-language pathologists can recommend the use of augmentative and alternative communication such as voice amplifiers, speech-generating devices (or voice output communication devices) and/or low tech communication techniques such as alphabet boards or yes/no signals.

### **Nutrition**

Patients and caregivers can learn from dietitians how to plan and prepare numerous small meals throughout the day that provide enough calories, fiber, and fluid and how to

avoid foods that are difficult to swallow. Patients may begin using suction devices to remove excess fluids or saliva and prevent choking. Occupational therapists can assist with recommendations for adaptive equipment to ease the physical task of self-feeding. Speech-language pathologists make food choice recommendations that are more conducive to their unique deficits and abilities.

When patients can no longer get enough nourishment from eating, doctors may advise inserting a feeding tube into the stomach. The use of a feeding tube also reduces the risk of choking and pneumonia that can result from inhaling liquids into the lungs. The tube is not painful and does not prevent patients from eating food orally if they wish. Researchers have stated, "ALS patients have a chronically deficient intake of energy and recommended augmentation of energy intake" and have a severe loss of appetite. Both animal and human research unreliable medical source?unreliable medical source? suggest that ALS patients should be encouraged to consume as many calories as possible and not to restrict their caloric intake. As of 2012, "a lack of robust evidence for interventions" remained for the management of weight loss.

### **Palliative care**

Social workers and home care and hospice nurses help people with ALS, their families, and caregivers with the medical, emotional, and financial challenges of coping, particularly during the final stages of the disease. Social workers provide support such as assistance in obtaining financial aid, arranging durable power of attorney, preparing a living will, and finding support groups for patients and caregivers.

## **TREATMENT**

No cure has yet been found for ALS. However, the Food and Drug Administration (FDA) approved the first drug treatment for the disease—riluzole (Rilutek)—in 1995. Riluzole is believed to reduce damage to motor neurons by decreasing the release of glutamate. Clinical trials with ALS patients showed that riluzole prolongs survival by several months, mainly in those with difficulty swallowing. The drug also extends the time before an individual needs ventilation support. Riluzole does not reverse the damage already done to motor neurons, and persons taking the drug must be monitored for liver damage and other possible side effects. However, this first disease-specific therapy offers hope that the progression of ALS may one day be slowed by new medications or combinations of drugs.

Other treatments for ALS are designed to relieve symptoms and improve the quality of life for individuals with the disorder. This supportive care is best provided by multidisciplinary 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. Physicians can prescribe

medications to help reduce fatigue, ease muscle cramps, control spasticity, and reduce excess saliva and phlegm.

### SUMMARY AND CONCLUSION

Regardless of the part of the body first affected by the disease, muscle weakness and atrophy spread to other parts of the body as the disease progresses. Individuals have increasing problems with moving, swallowing, and speaking or forming words. Eventually people with ALS will not be able to stand or walk, get in or out of bed on their own, or use their hands and arms. In later stages of the disease, individuals have difficulty breathing as the muscles of the respiratory system weaken. Although ventilation support can ease problems with breathing and prolong survival, it does not affect the progression of ALS. Most people with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. However, about 10 percent of those individuals with ALS survive for 10 or more years.

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