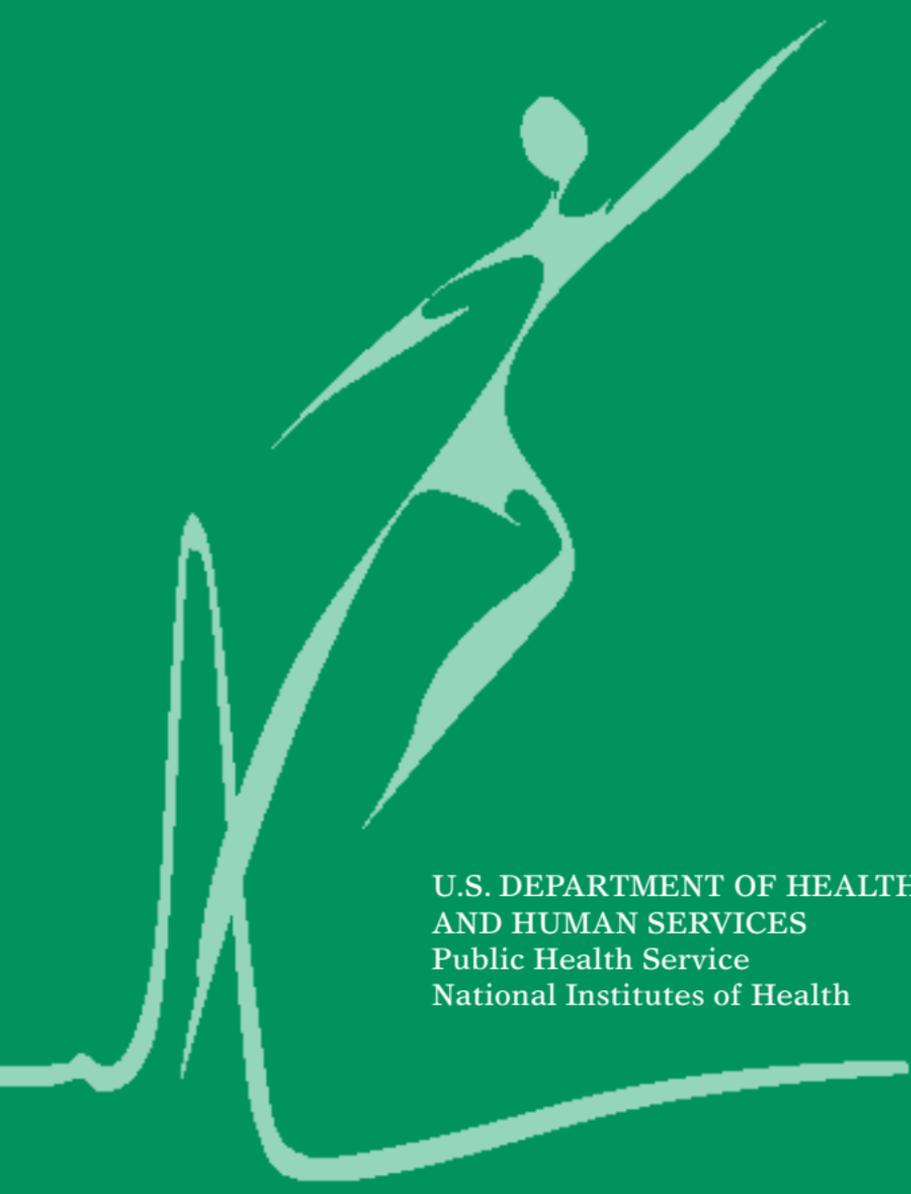


Amyotrophic Lateral Sclerosis



U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health



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What is amyotrophic lateral sclerosis?

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. Unable to function, the muscles gradually weaken, waste away (*atrophy*), and have very fine twitches (called *fasciculations*). Eventually, the ability of the brain to start and control voluntary movement is lost.

ALS causes weakness with a wide range of disabilities (see section titled “What are the symptoms?”). 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.

Who gets ALS?

As many as 20,000-30,000 people in the United States have ALS, and an estimated 5,000 people in the U.S. are diagnosed with the disease each year. ALS is one of the most common neuromuscular diseases worldwide, and people of all races and ethnic backgrounds are affected.

ALS most commonly strikes people between 40 and 60 years of age, but younger and older people also can develop the disease. Men are affected more often than women.

In 90 to 95 percent of all ALS cases, the disease occurs apparently at random with no clearly associated risk factors. Individuals with this sporadic form of the disease do not have a family history of ALS, and their family members are not considered to be at increased risk for developing it.

About 5 to 10 percent of all ALS cases are inherited. The familial form of ALS usually results from a pattern of inheritance that requires only one parent to carry the gene responsible for the disease. Mutations in more than a dozen genes have been found to cause familial ALS.

About one-third of all familial cases (and a small percentage of sporadic cases) result from a defect in a gene known as “chromosome 9 open reading frame 72,” or C9orf72. The function of this gene is still unknown. Another 20 percent of familial cases result from mutations in the gene that encodes the enzyme copper-zinc superoxide dismutase 1 (SOD1).

What are the symptoms?

The onset of ALS may be so subtle that the symptoms are overlooked. The earliest symptoms may include fasciculations, cramps, tight and stiff muscles (*spasticity*), muscle weakness affecting an arm or a leg, slurred and nasal speech, or difficulty chewing or

swallowing. These general complaints then develop into more obvious weakness or atrophy that may cause a physician to suspect ALS.

The parts of the body showing early symptoms of ALS depend on which muscles in the body are affected. Many individuals first see the effects of the disease in a hand or arm as they experience difficulty with simple tasks requiring manual dexterity such as buttoning a shirt, writing, or turning a key in a lock. In other cases, symptoms initially affect one of the legs, and people experience awkwardness when walking or running or they notice that they are tripping or stumbling more often. When symptoms begin in the arms or legs, it is referred to as “limb onset” ALS. Other individuals first notice speech problems, termed “bulbar onset” ALS.

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 may develop problems with moving, swallowing (*dysphagia*), and speaking or forming words (*dysarthria*). Symptoms of upper motor neuron involvement include spasticity and exaggerated reflexes (*hyperreflexia*) including an overactive gag reflex. An abnormal reflex commonly called Babinski’s sign (the large toe extends upward as the sole of the foot is stimulated in a certain way) also indicates upper motor neuron damage. Symptoms of lower motor neuron degeneration include muscle weakness and atrophy, muscle cramps, and fasciculations.

To be diagnosed with ALS, people must have signs and symptoms of both upper and lower motor neuron damage that cannot be attributed to other causes.

Although the sequence of emerging symptoms and the rate of disease progression vary from person to person, eventually individuals will not be able to stand or walk, get in or out of bed on their own, or use their hands and arms. Difficulty swallowing and chewing impair the person's ability to eat normally and increase the risk of choking. Maintaining weight will then become a problem. Because cognitive abilities are relatively intact, people are aware of their progressive loss of function and may become anxious and depressed. A small percentage of individuals may experience problems with memory or decision-making, and there is growing evidence that some may even develop a form of dementia over time. Health care professionals need to explain the course of the disease and describe available treatment options so that people can make informed decisions in advance. In later stages of the disease, individuals have difficulty breathing as the muscles of the respiratory system weaken. They eventually lose the ability to breathe on their own and must depend on ventilatory support for survival. Affected individuals also face an increased risk of pneumonia during later stages of ALS.

How is ALS diagnosed?

No one test can provide a definitive diagnosis of ALS, although the presence of upper and lower motor neuron signs is strongly suggestive. Instead, the diagnosis of ALS is primarily based on the symptoms and signs the physician observes in the patient and a series of tests to rule out other diseases. Physicians obtain the individual'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 getting progressively worse.

Since ALS symptoms in the early stages of the disease 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 is a *nerve conduction study* (NCS), which measures electrical energy by assessing the nerve's ability to send a signal). Specific abnormalities in the NCS and EMG may suggest, for example, that the individual has a form of peripheral neuropathy (damage to peripheral nerves) or myopathy (muscle disease) rather than ALS. The physician may order *magnetic resonance imaging* (MRI), a noninvasive procedure that uses a magnetic field and radio waves to take detailed images of the brain and spinal cord. Standard MRI scans are normal in

people with ALS. However, they can reveal evidence of other problems that may be causing the symptoms, such as a spinal cord tumor, a herniated disk in the neck that compresses the spinal cord, syringomyelia (a cyst in the spinal cord), or cervical spondylosis (abnormal wear affecting the spine in the neck).

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 that the individual may have a myopathy rather than ALS, a muscle biopsy may be performed.

Infectious diseases such as human immunodeficiency virus (HIV), human T-cell leukemia virus (HTLV), polio, West Nile virus, and Lyme disease can in some cases cause ALS-like symptoms. Neurological disorders such as multiple sclerosis, post-polio syndrome, multifocal motor neuropathy, and spinal muscular atrophy also can mimic certain facets of the disease and should be considered by physicians attempting to make a diagnosis. Fasciculations, the fine rippling movements in the muscle, and muscle cramps also occur in benign conditions.

Because of the prognosis carried by this diagnosis and the variety of diseases or disorders that can resemble ALS in the early stages of the disease, individuals may wish to obtain a second neurological opinion.

What causes ALS?

The cause of ALS is not known, and scientists do not yet know why ALS strikes some people and not others. An important step toward answering this question was made in 1993 when scientists supported by the National Institute of Neurological Disorders and Stroke (NINDS) discovered that mutations in the gene that produces the SOD1 enzyme were associated with some cases of familial ALS. Although it is still not clear how mutations in the SOD1 gene lead to motor neuron degeneration, there is increasing evidence that mutant SOD1 protein can become toxic.

Since then, over a dozen additional genetic mutations have been identified, many through NINDS-supported research, and each of these gene discoveries has provided new insights into possible mechanisms of ALS.

For example, the discovery of certain genetic mutations involved in ALS suggests that changes in the processing of RNA molecules (involved with functions including gene regulation and activity) may lead to ALS-related motor neuron degeneration. Other gene mutations implicate defects in protein recycling. And still others point to possible defects in the structure and shape of motor neurons, as well as increased susceptibility to environmental toxins.

Overall, it is becoming increasingly clear that a number of cellular defects can lead to motor neuron degeneration in ALS.

Another research advance was made in 2011 when scientists found that a defect in the C9orf72 gene is not only present in a significant subset of ALS patients but also in some patients who suffer from a type of frontotemporal dementia (FTD). This observation provides evidence for genetic ties between these two neurodegenerative disorders. In fact, some researchers are proposing that ALS and some forms of FTD are related disorders with genetic, clinical, and pathological overlap.

In searching for the cause of ALS, researchers are also studying the role of environmental factors such as exposure to toxic or infectious agents, as well as physical trauma or behavioral and occupational factors. For example, studies of populations of military personnel who were deployed to the Gulf region during the 1991 war show that those veterans were more likely to develop ALS compared to military personnel who were not in the region.

Future research may show that many factors, including a genetic predisposition, are involved in the development of ALS.

How is ALS treated?

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. Drugs also are available to help patients with pain, depression, sleep disturbances, and constipation. Pharmacists can give advice on the proper use of medications and monitor a patient's prescriptions to avoid risks of drug interactions.

Physical therapy and special equipment can enhance an individual's independence and safety throughout the course of ALS. Gentle, low-impact aerobic exercise such as 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 therapists can recommend exercises that provide these benefits without overworking muscles. Occupational therapists can suggest devices such as ramps, braces, walkers, and wheelchairs that help individuals conserve energy and remain mobile.

People with ALS who have difficulty speaking may benefit from working with a speech therapist. These health professionals can teach individuals adaptive strategies such as techniques to help them speak louder and more clearly. As ALS progresses, speech therapists can help people develop ways for responding to yes-or-no questions with their eyes or by other nonverbal means and can recommend aids such as speech synthesizers and computer-based communication systems.

These methods and devices help people communicate when they can no longer speak or produce vocal sounds.

Nutritional support is an important part of the care of people with ALS. Individuals and caregivers can learn from speech therapists and nutritionists 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. People may begin using suction devices to remove excess fluids or saliva and prevent choking. When individuals 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 individuals from eating food orally if they wish.

When the muscles that assist in breathing weaken, use of nocturnal ventilatory assistance (*intermittent positive pressure ventilation* [IPPV] or *bilevel positive airway pressure* [BIPAP]) may be used to aid breathing during sleep. Such devices artificially inflate the person's lungs from various external sources that are applied directly to the face or body. Individuals with ALS will have breathing tests on a regular basis to determine when to start non-invasive ventilation (NIV). When muscles are no longer able to maintain normal oxygen and carbon dioxide levels, these devices may be used full-time.

Individuals may eventually consider forms of mechanical ventilation (respirators) in which a machine inflates and deflates the lungs. To be effective, this may require a tube that passes from the nose or mouth to the windpipe (trachea) and for long-term use, an operation such as a tracheostomy, in which a plastic breathing tube is inserted directly in the patient's windpipe through an opening in the neck. Patients and their families should consider several factors when deciding whether and when to use one of these options. Ventilation devices differ in their effect on the person's quality of life and in cost. Although ventilation support can ease problems with breathing and prolong survival, it does not affect the progression of ALS. People need to be fully informed about these considerations and the long-term effects of life without movement before they make decisions about ventilation support.

Social workers and home care and hospice nurses help patients, families, and caregivers with the medical, emotional, and financial challenges of coping with ALS, particularly during the final stages of the disease.

Respiratory therapists can help caregivers with tasks such as operating and maintaining respirators, and home care nurses are available not only to provide medical care but also to teach caregivers about giving tube feedings and moving patients to avoid painful skin problems and contractures. Home hospice nurses work in consultation with physicians to ensure proper medication and pain control.

What research is being done?

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. The goals of this research are to find the cause or causes of ALS, understand the mechanisms involved in the progression of the disease, and develop effective treatments.

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, zebrafish, 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. Research in these models suggests that depending on the gene mutation, motor neuron death is caused by a variety of cellular defects, including in the processing of RNA molecules and recycling of proteins, as well as impaired energy metabolism, and hyperactivation of motor neurons. 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.

Overall, the work in familial ALS is already leading to a greater understanding of the more common sporadic form of the disease. Because familial ALS is virtually indistinguishable from sporadic ALS clinically, some researchers believe that familial ALS genes may also be involved in sporadic ALS. For example, 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.

Another active area of research is the development of innovative cell culture systems to serve as “patient-derived” model systems for ALS research. For example, scientists have developed ways of inducing skin cells from individuals with ALS into becoming pluripotent stem cells (cells that are capable of becoming all the different cell types of the body). 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. NINDS is supporting research on the development of pluripotent cell lines for a number of neurodegenerative diseases, including ALS.

Scientists are also working to develop biomarkers for ALS that could serve as tools for diagnosis, as markers of disease progression, or correlated with therapeutic targets. Such biomarkers can be molecules derived from a bodily fluid (such as spinal

fluid), an imaging assay of the brain or spinal cord, or an electrophysiological measure of nerve and muscle ability to process an electrical signal.

Potential therapies for ALS are being investigated in a range of animal models, especially in rodent models. This work involves the testing of drug-like compounds, gene therapy approaches, antibodies and cell-based therapies. In addition, at any given time, a number of exploratory treatments are in clinical testing in ALS patients. Investigators are optimistic that these and other basic, translational, and clinical research studies will eventually lead to new and more effective treatments for ALS.

How can I help research?

The NINDS and the Centers of Disease Control and Prevention/ Agency for Toxic Substances and Disease Registry (CDC/ ATSDR) are committed to studies of disease patterns or risk factors among persons with ALS in order to better understand the causes of ALS, the mechanisms involved in the progression of the disease, and to develop effective treatments. The National ALS Registry, a program to collect, manage, and analyze data about persons with ALS, was launched in October 2010 and is actively enrolling individuals with the disease. The Registry includes data from national databases as well as de-identified information provided by persons with ALS. All collected information is kept confidential. Persons

living with ALS who choose to participate can add their information to the Registry by visiting www.cdc.gov/als.

Clinical trials offer hope for many people and an opportunity to help researchers find better ways to safely detect, treat, or prevent disease. Many neurological disorders don't have good treatment options. By participating in a clinical trial, individuals with an illness or disease can greatly affect their life and those of others affected by a neurological disorder. For information about finding and participating in clinical trials, visit NIH Clinical Research Trials and You at www.nih.gov/health/clinicaltrials. Use the search terms "amyotrophic lateral sclerosis" or "ALS AND (your state)" to locate trials in your area.

The NINDS contributes to the support of the Human Brain and Spinal Fluid Resource Center in Los Angeles. This bank supplies investigators around the world with tissue from patients with neurological and other disorders. Tissue from individuals with ALS is needed to enable scientists to study this disorder more intensely. Prospective donors may contact:

Human Brain and Spinal Fluid Resource Center

Neurology Research

W. Los Angeles Healthcare Center

11301 Wilshire Blvd. (127A)

Building 212, Room 16

Los Angeles, CA 90073

310-268-3536

www.brainbank.ucla.edu

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN

P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Information also is available from the following organizations:

The ALS Association

1275 K Street, N.W., Suite 1050
Washington, DC 20005
202-407-8580
800-782-4747
www.alsa.org

ALS Therapy Development Institute

300 Technology Square, Suite 400
Cambridge, MA 02139
617-441-7200
www.als.net

Les Turner ALS Foundation

5550 West Touhy Avenue, Suite 302
Skokie, IL 60077-3254
847-679-3311
888-257-1107
www.lesturnerals.org

Muscular Dystrophy Association

3300 East Sunrise Drive

Tucson, AZ 85718-3208

800-572-1717

www.mda.org

PRIZE4LIFE

P.O. Box 425783

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