

Review Article

A Comprehensive Review on Amyotrophic Lateral Sclerosis

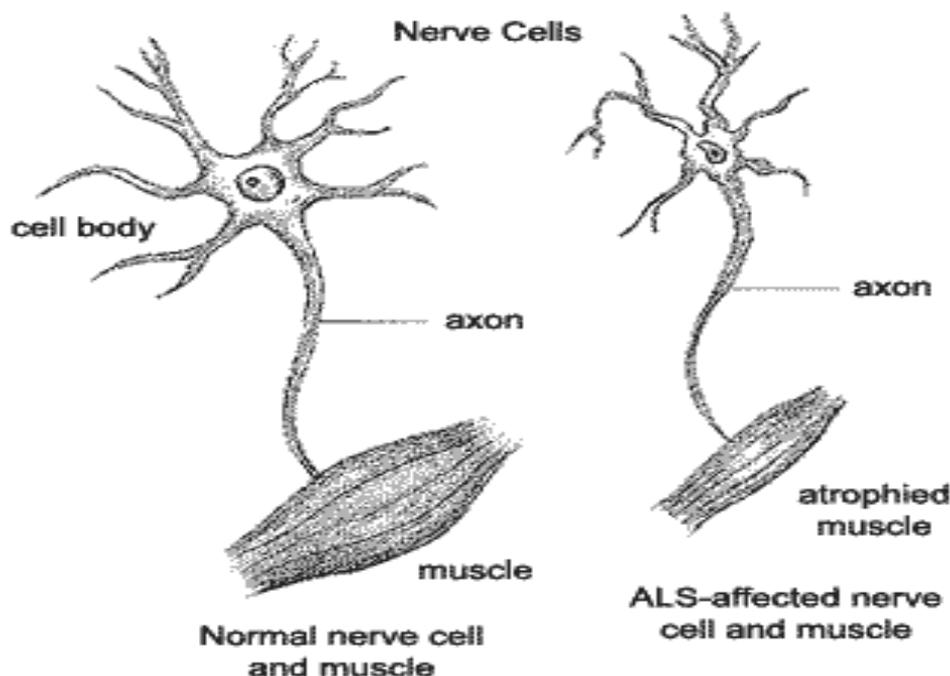
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ABSTRACT

Amyotrophic lateral sclerosis (ALS) – also referred to as motor neurone disease in some Commonwealth of Nations countries and as Lou Gehrig's disease in the United States – is a debilitating disease with varied etiology characterized by rapidly progressive weakness, muscle atrophy and fasciculations, muscle spasticity, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), and difficulty breathing (dyspnea). ALS is the most common of the five motor neuron diseases¹. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Motor neurons reach from the brain to the spinal cord and from the spinal cord to the muscles throughout the body. The progressive degeneration of the motor neurons in ALS eventually leads to their death. When the motor neurons die, the ability of the brain to initiate and control muscle movement is lost. With voluntary muscle action progressively affected, patients in the later stages of the disease may become totally paralyzed. A-myo-trophic comes from the Greek language. "A" means no or negative. "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. As motor neurons degenerate, they can no longer send impulses to the muscle fibers that normally result in muscle movement. Early symptoms of ALS often include increasing muscle weakness, especially involving the arms and legs, speech, swallowing or breathing. When muscles no longer receive the messages from the motor neurons that they require to function, the muscles begin to atrophy (become smaller). Limbs begin to look "thinner" as muscle tissue atrophies².

INTRODUCTION



The body has many kinds of nerves. There are those involved in the process of thinking, memory, and of detecting sensations (such as hot/cold, sharp/dull), and others for vision, hearing, and other bodily functions. The nerves that are affected when you have ALS are the motor neurons that provide **voluntary movements** and **muscle power**. Examples of voluntary movements are your making the effort to reach for the phone or step off a curb; these actions are controlled by the muscles in the arms and legs.

The heart and the digestive system are also made of muscle but a different kind, and their movements are not under voluntary control. When your heart beats or a meal is digested, it all happens automatically. Therefore, the heart and digestive system are not involved in ALS. Breathing also may seem to be involuntary. Remember, though, while you cannot stop your heart, you can hold your breath - so be aware that ALS may eventually have an impact on breathing.

Although the cause of ALS is not completely understood, the recent years have brought a wealth of new scientific understanding regarding the physiology of this disease.

While there is not a cure or treatment today that halts or reverses ALS, there is one FDA approved drug, riluzole, that modestly slows the progression of ALS as well as several other drugs in clinical trials that hold promise. Importantly, there are significant devices and therapies that can manage the symptoms of ALS that help people maintain as much independence as possible and prolong survival. It is important to remember that ALS is a quite variable disease; no two people will have the same journey or experiences. There are medically documented cases of people in whom ALS 'burns out,' stops progressing or progresses at a very slow rate. No matter what your individual course or situation may be, The ALS Association and your medical team are here to help³.

Epidemiology

The incidence of sporadic amyotrophic lateral sclerosis (SALS) in the 1990's is reported to be between 1.5 and 2.7 per 100,000 population/year (average 1.89 per 100,000/year) in Europe and North America, with a uniform incidence across these countries. The point prevalence in the 1990's ranges from 2.7 to 7.4 per 100,000 (average 5.2 per 100,000) in western countries. The lifetime risk of SALS by the age of 70 has been estimated at 1 in 1,000 but a more accurate estimate is more likely to be 1 in 400. A consistent finding in studies is that there is a

slight excess of males are affected more than females, with a M:F ratio about 1.5:1, although more recent data suggests that the gender ratio may be approaching equality. Explanations for this male excess have been attributed to possible protective hormonal factors in women, increased likelihood of males being exposed to putative risk factors and under ascertainment of elderly women in some population registers. A review published in 2001 found the mortality rates of ALS in the 1990's ranged from 1.54 to 2.55 per 100,000/year and a more recent study estimated the figure to be 1.84 per 100,000 persons in the US population. The mean age of onset for sporadic ALS (SALS) varies between 55-65 years with a median age of onset of 64 years. Only 5% of cases have an onset before the age of 30 years, although juvenile sporadic onset cases are being increasingly recognized. Bulbar onset is commoner in women and in older age groups, with 43% of patients over the age of 70 presenting with bulbar symptoms compared to 15% below the age of 30. Although most cases of ALS are sporadic, about 5% of cases have a family history of ALS (Familial ALS; FALS). There is an often Mendelian inheritance and high penetrance, with most cases having autosomal dominant pattern of inheritance, although autosomal recessive pedigrees have been reported. The ages of onset of FALS is about a decade earlier than for sporadic cases, affects males and female equally, and have a shorter survival. Age of onset in FALS has a normal Gaussian distribution, whereas SALS has an age dependant incidence. Juvenile onset ALS (jALS) is a term used when age of onset is less than 25 years. Most cases are autosomal recessive although dominant inheritance linked to chromosome 9q34 (ALS4, *senataxin*) has been reported. Recessive forms have been mapped to chromosome regions 2q33 (ALS2, *alsin*), and 15q12-21.

Geographic loci of the Western Pacific form of ALS, where the prevalence is 50-100 times higher than elsewhere world have been reported, although the cause of these aggregations remains elusive. These populations include the Chamorro people of Guam and Marianas island, the Kii peninsula of Honshu Island, and the Auyu and Jakai people of south west New Guinea, in whom ALS is associated with the Parkinsonism and dementia (ALS-PD complex). More recent studies however have shown a decrease in incidence of both ALS and PDC in these areas over the past 40 years, although the incidence

of PDC slightly increased during the eighties and nineties⁴.

Pathogenesis

Although the cause of ALS is unknown, genetic inheritance plays a role in 5% to 10% of cases. A fraction of all cases of familial ALS (that is, inherited ALS) is believed to be caused by a defective gene that prevents the body from producing a normal amount of an enzyme called superoxide dismutase. This enzyme helps neutralize free radicals -- highly reactive oxygen molecules produced during metabolism and capable of damaging body tissues. Researchers speculate that defects in protective enzymes may also account for noninherited ALS and that environmental toxins may be a factor.

Some evidence suggests that the disease may be triggered by exposure to heavy metals, animal hides, or fertilizers, although this is by no means proven. In addition, viral infection and severe physical trauma have been implicated as possible contributors. Other theories link ALS to a phenomenon called excitotoxicity, in which the nerve cells that control movement are so relentlessly stimulated by a neurotransmitter called glutamate that they eventually die⁵.

Diagnose

No one test can provide a definitive 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 patient and a series of tests to rule out other diseases. Physicians obtain the patient'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.

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. 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. Although these MRI scans are often normal in patients with ALS, 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, syringomyelia, or cervical spondylosis.

Based on the patient'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 patient 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), 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.

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, patients may wish to obtain a second neurological opinion⁶.

Treatment

No cure has yet been found for ALS. However, the Food and Drug Administration (FDA) has approved the first drug treatment for the disease—riluzole (Rilutek). 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 a patient needs ventilation support. Riluzole does not reverse the damage already done to motor neurons, and patients 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 patients. This supportive care is best provided by multidisciplinary teams of health care professionals such as physicians; pharmacists; physical, occupational, and speech therapists; nutritionists; 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 possible⁷.

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 patients' 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 patients conserve energy and remain mobile.

ALS patients who have difficulty speaking may benefit from working with a speech therapist. These health professionals can teach patients adaptive strategies such as techniques to help them speak louder and more clearly. As ALS progresses, speech therapists can help patients 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 systems⁸. These methods and devices help patients communicate when they can no longer speak or produce vocal sounds.

CONCLUSION

ALS is a very serious neurological disease that affects the body's ability to control voluntary muscles, there are no cure for ALS, however research and new forms of treatments are being developed. knowing about ALS and its progression will help patients make informed decision concerning their health care. The remaining treatment options are to treat the symptoms. First and foremost, good nutrition

is essential so that the body does not use the remaining healthy tissue for fuel. Several medications are available to help control muscle spasms, leg cramps and contractions. As the control of the hands and feet are lost, special grips, utensils, devices and braces are available to extend functionality. Also communication devices can be useful in helping the individual to communicate with others. The ability to communicate with others also aids in combating feelings of isolation and depression. As breathing becomes more labored, a number of devices are available to assist the individual.

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