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REVIEW

# Pathophysiology of amyotrophic lateral sclerosis

## Fisiopatología de la esclerosis lateral amiotrófica

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## ABSTRACT

**Introduction:** neurodegenerative diseases are hereditary or acquired pathologies that cause progressive dysfunction of the central nervous system. Amyotrophic lateral sclerosis is the most important of the degenerative diseases that can affect motor neurons. The disease is inexorably progressive and leads to death by respiratory paralysis.
**Objective:** to characterize the evolution and general features of amyotrophic lateral sclerosis.
**Method:** a search was conducted in Medline, Pubmed, and Google Scholar, limited to Spanish and English, and documents published mainly in the last five years were selected. However, due to their interest, several papers prior to the established time limit were included. Sixteen papers were included in the review, representing a 62,5 % update.
**Development:** in most patients, risk factors for this disease cannot be identified. Symptoms generally do not appear until after the age of 50. In diagnosing this disease, the neurologist must perform a clinical examination and a series of tests to rule out other diseases that mimic ALS. Although there is no cure, the symptoms can be treated to seek the best possible quality of life.
**Conclusions:** amyotrophic lateral sclerosis affects adults of any race or ethnicity. When the muscles of the diaphragm and chest wall fail, breathing becomes impossible without the aid of artificial ventilation. Treatment should be multidisciplinary, offering all patients the opportunity to receive riluzole.

**Keywords:** Neurodegenerative Diseases; Amyotrophic Lateral Sclerosis; Pathophysiology.

## RESUMEN

**Introducción:** las enfermedades neurodegenerativas son aquellas patologías, hereditarias o adquiridas, en las que se produce una disfunción progresiva del sistema nervioso central. La esclerosis lateral amiotrófica es la más importante de las degeneraciones que pueden afectar a las motoneuronas. La enfermedad es inexorablemente progresiva y conduce a la muerte por parálisis respiratoria.
**Objetivo:** caracterizar la evolución y generalidades de la esclerosis lateral amiotrófica.
**Método:** se realizó una búsqueda en Medline, Pubmed y Google académico que fue delimitada por idioma (español e inglés), y se seleccionaron aquellos documentos publicados principalmente en los últimos 5 años. Sin embargo, por su interés, fueron incluidos varios artículos anteriores al límite temporal establecido. Se incluyeron en la revisión 16 artículos, siendo un 62,5 % de actualización.
**Desarrollo:** en la mayoría de los pacientes no puede identificarse factores de riesgo para esta enfermedad. Los síntomas generalmente no se presentan sino hasta después de los 50 años. En el diagnóstico de esta enfermedad, el neurólogo debe realizar un examen clínico y una serie de pruebas que descartan otras

enfermedades que imiten a la ELA. Aunque no tiene cura, se pueden tratar los síntomas para buscar la mejor calidad de vida posible.
**Conclusiones:** la esclerosis lateral amiotrófica afecta a personas adultas de cualquier raza y etnia. Cuando fallan los músculos del diafragma y de la pared torácica, la respiración resulta imposible sin el auxilio de la ventilación artificial. El tratamiento debe ser multidisciplinario ofreciendo a todos los pacientes la oportunidad de recibir el riluzol.

**Palabras clave:** Enfermedades Neurodegenerativas; Esclerosis Lateral Amiotrófica; Fisiopatología.

## INTRODUCTION

The nervous system is made up of interconnected central and peripheral structures that form an indivisible unit. It extends throughout the body through the peripheral nerves, directly influencing other systems, collecting stimuli, and promoting their actions.

Its most distal structures are the receptors, which respond to internal and external stimuli, converting them into electrical signals conducted through the peripheral nerves to more complex structures belonging to the central nervous system.[1]

The nervous system controls movement through the action of peripheral motor nerves on the muscles. Sensory areas, motor centres, and associative centres can be identified in the central structures. The direct connection between the sensory and motor systems ensures the coupling between stimuli and responses, which are generally reflexive and predictable.[1]

Neurodegenerative diseases are hereditary or acquired pathologies in which there is progressive dysfunction of the central nervous system (CNS). Most of these diseases are characterised by a common pathogenic mechanism consisting of the aggregation and accumulation of misfolded proteins that are deposited in the form of intracellular or extracellular aggregates and cause cell death. Each disease is characterised by selective neuronal vulnerability at the CNS level, which leads to the degeneration of specific areas, producing the corresponding symptoms of loss of function.[2]

These nervous system diseases are characterised by alterations in the cognitive, emotional, and behavioural functioning of those affected. Some are particularly prevalent in our context and represent a serious health problem. Although not all are associated with ageing, this is often a relevant risk factor.[2]

Amyotrophic lateral sclerosis (ALS) is the most important of the degenerative diseases that can affect motor neurons. When these neurons degenerate, they lose their ability to stimulate the muscles, which become weak or paralysed and, in turn, become thin or "atrophied".[3]

Jean-Martin Charcot was the world's first professor of neurology, awarded the title of nervous diseases by the Salpêtrière Hospital in 1882. Charcot's contributions to the understanding of neurological diseases are numerous. In addition to being the first to define amyotrophic lateral sclerosis in 1869 as a sporadic adult disease resulting from the progressive idiopathic degeneration of the motor neuron system, including the upper motor neurons in the motor cortex and their corticobulbar and corticospinal projections, and the lower motor neurons and their projections in the peripheral nerve trunks, resulting in generalised, progressive and rapid muscle weakness and atrophy, often leading to death. Charcot named it thus because he found the lateral corticospinal tracts degenerated, hard, and whitish (lateral sclerosis) in patients with severe muscle wasting (amyotrophic). In British Commonwealth countries, this condition became known as 'motor neuron disease' after its description by Brain and Walton in 1969.[3,4]

The disease is inexorably progressive and leads to death by respiratory paralysis, with an average survival of between three and five years. The progressive deterioration of ALS patients has a significant impact on their quality of life. Its incidence increases after the age of 50. A few rare cases of stabilisation or even regression of ALS have been reported. In most societies, there is an incidence of one to three new cases per 100 000 inhabitants and a prevalence of three to six per 100 000 inhabitants.[5]

Worldwide, the annual incidence is around a crude rate of 1,75/100 000 inhabitants and a standardised rate for the world population of 1,68/100 000. Incidence and prevalence are lower in populations of 'mixed' origin than in European or European ancestry populations.[6]

About 10 % of patients have a hereditary pattern. The age range of onset is 58 to 63 years for sporadic cases and 47 to 52 years for familial cases, with a slight predilection for males. It has been reported that 5,600 people are diagnosed with ALS annually in the United States.[7,8]

Population-based epidemiological studies of ALS are very scarce in Latin America.[8] In Cuba, one of the few studies conducted on ALS is that developed by Serra Ruiz M and Serra Valdés MA5, which characterises the survival of patients with ALS in a hospital in Havana, Cuba.

Recent scientific advances have improved our understanding of this disease, but many questions remain

unanswered. In the 160-year history of ALS, there is still no effective treatment for the disease despite more than 200 clinical trials conducted by over 60 different institutions and companies worldwide. This disease causes significant changes in family structure and dynamics due to the emotional, psychological, and economic problems it entails. The issues described above motivated us to conduct a literature review on the subject.

**Objective:** To characterise the evolution and general features of amyotrophic lateral sclerosis.

## METHOD

Between September and December 2021, a systematic literature search was conducted in textbooks and periodicals on the pathophysiology of amyotrophic lateral sclerosis. A maximum retrospective period of 10 years was established for textbooks and five years for journals. However, articles before the established time limit were included due to their interest.

The electronic search was conducted on Medline, PubMed, and Google Scholar. The following keywords were used: amyotrophic lateral sclerosis and pathophysiology.

Fifty-four references in Spanish and English were obtained that responded to the established keywords, of which 31 were selected after preliminary analysis based on their titles. Subsequently, 16 scientific articles from periodicals (62,5 % update) were chosen to form the body of the literature review.

The documents selected for the review were organised chronologically and analysed independently. A summary sheet was prepared for each of them, which was used as a theoretical framework.

## DEVELOPMENT

Many authors define amyotrophic lateral sclerosis as a progressive neurodegenerative syndrome that belongs to the group of motor neuron diseases. Its aetiopathogenesis remains unclear.

ALS cases can be classified into two types: sporadic ALS (most cases fall into this group, i.e., between 90 and 95 % of cases) and familial ALS, which is due to genetic inheritance. Several researchers have also suggested that it can affect two different levels: upper motor neurons or first motor neurons (found in the spinal cord, at the level of the cortex and motor nuclei) and lower motor neurons or second motor neurons (found in the ventral horn of the spinal cord).[7,9]

In most patients, no risk factors can be identified. The broad spectrum of possible causes includes, among others, the following: oxidative stress, genetic factors, glutamate excitotoxicity, mitochondrial damage, axonal transport defect, damage caused by astrocytes, apoptosis, intense physical activity, military service, exposure to radiation and toxins, and a combination of these factors.[5,7]

The Francisco Luzón Foundation[10] suggests that increased physical activity or situations of particular stress are considered triggers of the disease rather than risk factors; however, Zapata et al.[7] suggest that physical activity is not a risk factor for developing this disease and that other variables should be analysed.

In any case, the currently proposed risk factors are inconclusive, and healthcare professionals do not know the characteristics of people who are most likely to develop the disease, which significantly hinders the implementation of preventive or early detection measures.

The research team believes that, although years have passed since the discovery of the disease, its cause remains unknown, and research should continue until it is clarified.

Symptoms do not usually appear until age 50, but can start in younger people. People with this condition experience a loss of muscle strength and coordination that worsens over time, making it impossible for them to perform routine activities such as climbing stairs, getting up from a chair, or swallowing. Weakness may first affect the arms or legs, or the ability to breathe or swallow. As the disease worsens, more muscle groups develop problems. Many of these symptoms are easily attributable to other diseases, significantly complicating diagnosis, as professionals confuse them with different conditions. ALS does not affect the senses (sight, smell, taste, hearing, or touch). Most people can think as they usually do, although a small number develop dementia, which causes memory problems.[10,11]

According to the Francisco Luzón Foundation,[10] as there is no single test to help diagnose ALS, the neurologist must make a differential diagnosis, which consists of a clinical examination and a series of tests to rule out other diseases that mimic ALS, until a diagnosis is established through the elimination of other possible diseases. However, Navarro Rando M.[9] explains that the primary diagnostic test for ALS is electromyography (EMG), which consists of recording the voltage changes that occur in muscle fibres during the depolarisation of their membranes during voluntary or spontaneous contraction.

The physical examination may show:[11]

- Weakness, often starting in one area
- Muscle tremors, spasms, fasciculations, or loss of muscle tissue
- Tongue fasciculations (common)
- Abnormal reflexes
- Rigid or clumsy gait

- Increased or decreased reflexes in the joints
- Difficulty controlling crying or laughing (sometimes called emotional incontinence)
- Loss of gag reflex

Tests that may be done in addition to electromyography include:[11]

- Blood tests to rule out other conditions
- Breathing test to see if the muscles of the lungs are affected
- Magnetic resonance imaging (MRI) or computed tomography (CT) scan of the cervical spine to check for any disease or injury in the neck that could appear to be ALS
- Genetic testing if there is a family history of ALS
- CT scan or MRI of the head to rule out other conditions
- Swallowing studies
- Spinal tap (lumbar puncture)

The low incidence of ALS means that many professionals are not sufficiently familiar with the disease and therefore do not consider it in their diagnosis, as many more prevalent diseases produce symptoms similar to ALS.[10]

Carrasco Márquez D[12] states that, specifically, a large proportion of familial ALS cases have been linked to mutations in SOD1, approximately 1 in 5 cases. Three other genes, called TARDBP, FUS, and C9orf72, have recently been described as being related to familial ALS and associated with the potential dysregulation of RNA processing in the pathogenesis of ALS.[12]

The research team suggests that it is essential to make a differential diagnosis when diagnosing ALS because its clinical manifestations can be confused with other diseases that affect the central nervous system.

Among the main genes involved in the development of ALS, the following are noteworthy:[12]

- SOD1 is an enzyme that eliminates free radicals, converting superoxide anions into hydrogen peroxide. It belongs to the group of enzymes called Cu/Zn (copper/zinc) metalloenzymes.
- TARDBP (Tar DNA binding protein), whose mutation has been linked to the development of ALS due to the formation of abnormal aggregates of the TDP-43 protein in neurons and glial cells in the spinal cord of patients with familial and sporadic ALS
- -C90RF72 (chromosome 9 open Reading frame 72) is a gene linked to ALS through the elongation of a nucleotide sequence in a non-coding region of chromosome 9. This mutation is present in 25-40 % of cases of familial ALS. The importance of this mutation was discovered thanks to studies that showed that ALS and FTD (frontotemporal dementia) were inherited together
- Other genes related to the onset of ALS are: VAPB (vesicle-associated membrane protein B), FUS (fused in sarcoma), UBQLN2 (ubiquilin 2), HNRNPA1, and HNRNPA2B1 (heterogeneous nuclear ribonucleoproteins A1 and A2/B1)

The SOD1 mutation increases the formation of harmful ·OH radicals and their peroxynitrite derivatives. These intracellular free radicals affect mitochondrial proteins and DNA and inhibit specific mitochondrial enzyme activities in the mitochondrial electron transport chain. In mice with the SOD1 mutation, oxidative damage has been observed in neural tissue. Still, several studies have found that if the mutation was only present in this tissue, the ALS phenotype did not occur. Therefore, with other human mutations (SODG93A, SOD1G85R, and SOD1G37R), it has been proposed that ALS is a multisystemic disease.

In patients with mutations in the TDP43 and FUS/TLS genes, they bind to RNA and DNA and move between the nucleus and the cytoplasm, performing multiple functions in the control of cell proliferation, DNA repair and transcription, and gene translation, both in the cytoplasm and the dendritic spines, in response to electrical activity. Another hypothesis is that TDP-43 normally functions by repressing the splicing of non-conserved regions of the genome, known as cryptic exons. The depletion or aggregation of TDP-43 allows the splicing of cryptic exons in messenger RNA, which disrupts translation and leads to cell death. The cause of how mutations in FUS/TLS lead to motor neuron death is unknown, although this may be represented by a loss of FUS/TLS function in the nucleus or an acquired toxic function of mutant proteins in the cytosol.

Immune system activation has been observed in ALS patients in peripheral blood and cerebrospinal fluid. Neuroinflammation in ALS is essential in the pathophysiology of the disease, as demonstrated by the presence of activated microglia and lymphocytic infiltration in the central nervous system, specifically in areas where neuronal damage has occurred. It has been shown that, in ALS, microglial cells and astrocytes interact with each other, contributing to the progression of the disease. In the early stages of the disease, the immune system promotes the regeneration of damaged neurons; however, as the disease progresses, the effect of activated T cells can be harmful, eliminating damaged neurons instead of contributing to their repair.

Although there is no cure for this disease, the symptoms can be treated to improve quality of life as much as

possible. To this end, the assistance that multidisciplinary teams can provide these patients is essential. Current efforts are focused on delaying the disease, improving the quality of life of ALS patients, and minimizing the side effects of the progressive deterioration of their motor function.[14]

The United States Food and Drug Administration (FDA) has only approved two drugs for the treatment of amyotrophic lateral sclerosis

- Riluzole was approved in the early 1990s.
- Edaravone was approved decades later, in 2017.

Riluzole is a drug belonging to the benzothiazole family, specifically a glutamate antagonist antioxidant. Although studies emphasise that the mechanism of action of riluzole against amyotrophic lateral sclerosis has not yet been clarified, it has been suggested that its function is to block the excessive release of glutamate in motor neurons because uncontrolled secretion of glutamate in synaptic junctions overstimulates signal reception by this type of neuron, leading to higher than normal levels of calcium in the soma of motor neurons and glial cells. These high calcium levels cause lipid membrane peroxidation, RNA and DNA damage, and disruption of mitochondrial activity, leading to cell death. Another essential finding regarding riluzole is that it protects cells from oxidative stress. However, another study has shown that this drug is not effective on its own, but may have a synergistic effect when used in combination with other medications, such as edaravone. Edaravone is defined in the studies conducted as a drug developed by Mitsubishi Tanabe Pharma with an antioxidant effect because it reduces the number of free radicals. The FDA approved it after demonstrating its effectiveness in slowing the progression of the disease in its early stages.

Riluzole is of great theoretical and practical interest. Still, it is unknown whether improved survival occurs throughout the disease or only at certain stages, mainly in young patients with a short time since diagnosis and a spinal clinical form.

Physiotherapy, rehabilitation, and the use of orthopaedic devices or wheelchairs, or other orthopaedic measures may be necessary to maximise muscle function and overall health. People with ALS tend to lose weight. The disease itself increases the need for food and calories. At the same time, problems with choking and swallowing make it difficult to eat enough. To help with feeding, a tube may be placed in the stomach. A nutritionist who specialises in ALS can offer advice on healthy eating. Breathing devices include machines used only at night and constant mechanical ventilation. Medications for depression may be needed if a person with ALS feels sad.[11]

The authors consider that although ALS has no cure, drug treatment with riluzole and edaravone, in addition to physiotherapy and rehabilitation, is essential to improve the quality of life of patients suffering from this disease.

Respiratory failure is the leading cause of death in patients with ALS. Non-invasive ventilation (NIV) is an effective therapeutic measure for this condition; bi-level positive pressure ventilation (BiPAP) is the most physiological method. International guidelines recommend its prescription in the presence of symptoms related to respiratory failure associated with one of the following findings (59): PaCO2 greater than 45 mm Hg, vital capacity less than 50 % of normal, maximum inspiratory pressure below 60 % of normal, nocturnal desaturation of PaO2 below 90 % more than 5 % of the time. NIV and secretion aspiration improve sleep quality and cognitive function, prolong survival, and improve quality of life.[7]

Stephen Hawking is undoubtedly the best-known and most extraordinary case of amyotrophic lateral sclerosis. Although the British physicist was diagnosed at age 21 and lived to be 76, those who suffer from the disease usually die within five to 10 years after symptoms appear.[16]

## CONCLUSIONS

Amyotrophic lateral sclerosis is characterised by rapid clinical deterioration and selective death of motor neurons in the cerebral cortex, brain stem, and spinal cord. ALS affects adults of any race or ethnicity. The cause of motor neuron death in these patients is unknown. When the muscles of the diaphragm and chest wall fail, breathing becomes impossible without the aid of artificial ventilation. Treatment should be multidisciplinary, offering all patients the opportunity to receive riluzole.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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