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# AMYOTROPHIC LATERAL SCLEROSIS (ALS) – A TYPICAL MOTOR NEURON DISEASE: A BRIEF REVIEW

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## ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a genetically diverse disease. At least 15 ALS-associated gene loci have so far been identified, and the causative gene is known in approximately 30% of familial ALS cases.Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that results in progressive loss of bulbar and limb function. Patients typically die from respiratory failure within 3 years of symptom onset. The incidence of ALS in Europe is 2–3 cases per 100,000 individuals in the general population, and the overall lifetime risk of developing the disease is 1:400. ALS is familial in 5% of cases, and shows a Mendelian pattern of inheritance. ALS is recognized to overlap with frontotemporal dementia. Diagnosis is made on clinical grounds, using internationally recognized consensus criteria, after exclusion of conditions that can mimic ALS. The Revised ALS Functional Rating Scale is currently the most widely used assessment tool; scores are used to predict survival, and have been employed extensively in clinical trials. Riluzole remains the only effective drug, and extends the average survival of patients by 3–6 months. Optimal treatment is based on symptom management and preservation of quality of life, provided in a multidisciplinary setting. The discovery of further effective disease-modifying therapies remains a critical need for patients with this devastating condition.

**KEYWORDS:** Cases.Amyotrophic, Mendelian, frontotemporal.

## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is one of the motor neuron diseases. In the USA it is commonly known as Lou Gehrig's disease, after the baseball player diagnosed with this

disease in 1939. The clinical features of ALS are those of progressive neurological deterioration involving the corticospinal tract, brainstem and anterior horn cells of the spinal cord.[1, 2] Clinical, pathological and genetic advances indicate heterogeneity in phenotype, pathological substrate and genetic predisposition, suggesting that ALS should be considered a syndrome rather than a single disease entity.[3–4] Although the clinical presentation and progression of ALS varies considerably, the course is inexorably progressive, and over 60% of patients die within 3 years of presentation. Of the remaining patients, up to 10% survive for more than 8 years.2 ALS is familial in 5% of cases, and shows a Mendelian pattern of inheritance.[5] The clinical phenotype of familial ALS is similar to that of the sporadic form of the disease. At least 15 genes have been associated with the various types of familial ALS, and variants in these genes account for 30% of these cases. Sporadic ALS is considered to be a complex disease, in which genetic and environmental factors combine to increase the risk of developing the condition.[6] Identification of these genetic and environmental risks has been challenging owing to a combination of factors, including the relatively low incidence rate of ALS, disease heterogeneity, genetic diversity across populations, and reduced penetrance of some mutations.

The establishment of multidisciplinary ALS clinics and the development of population-based ALS registers have begun to present rich clinical, genotype and epidemio logical data that can help to provide insights into this heterogeneous disease.[7] In this Review, we provide an over view of key advances in understanding of the epidemiology, clinical features, diagnosis and management of this devastating disease.

**KEY POINTS**

Amyotrophic lateral sclerosis (ALS) is a syndrome of progressive deterioration involving the corticospinal tract, brainstem, and anterior horn cells of the spinal cord

■ The risk of developing ALS peaks between the ages of 50 years and 75 years; disease rates are elevated in populations of white European ancestry, and reduced in mixed populations

■ No definitive test for ALS exists; the diagnosis is established by excluding other causes of progressive upper motor neuron and lower motor neuron dysfunction

■ Up to 15% of patients with ALS have frontotemporal dementia, and a further 25% have evidence of cognitive impairment, mainly executive dysfunction

■ Clinical care is based on symptom management; however, riluzole, the only available disease-modifying drug, improves patients' survival early in the course of the disease

■ Further improvements in survival will depend on advances in understanding the origins and spread of this syndrome

**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.[8] 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.[9,10] but a more accurate estimate is more likely to be 1 in 400,[11,12] 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.[13,14] 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.[15,16] 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.[17] The mean age of onset for sporadic ALS (SALS) varies between 55–65 years with a median age of onset of 64 years.[18, 19] Only 5% of cases have an onset before the age of 30 years,[20] although juvenile sporadic onset cases are being increasingly recognised.[21] 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.[22,23,24]

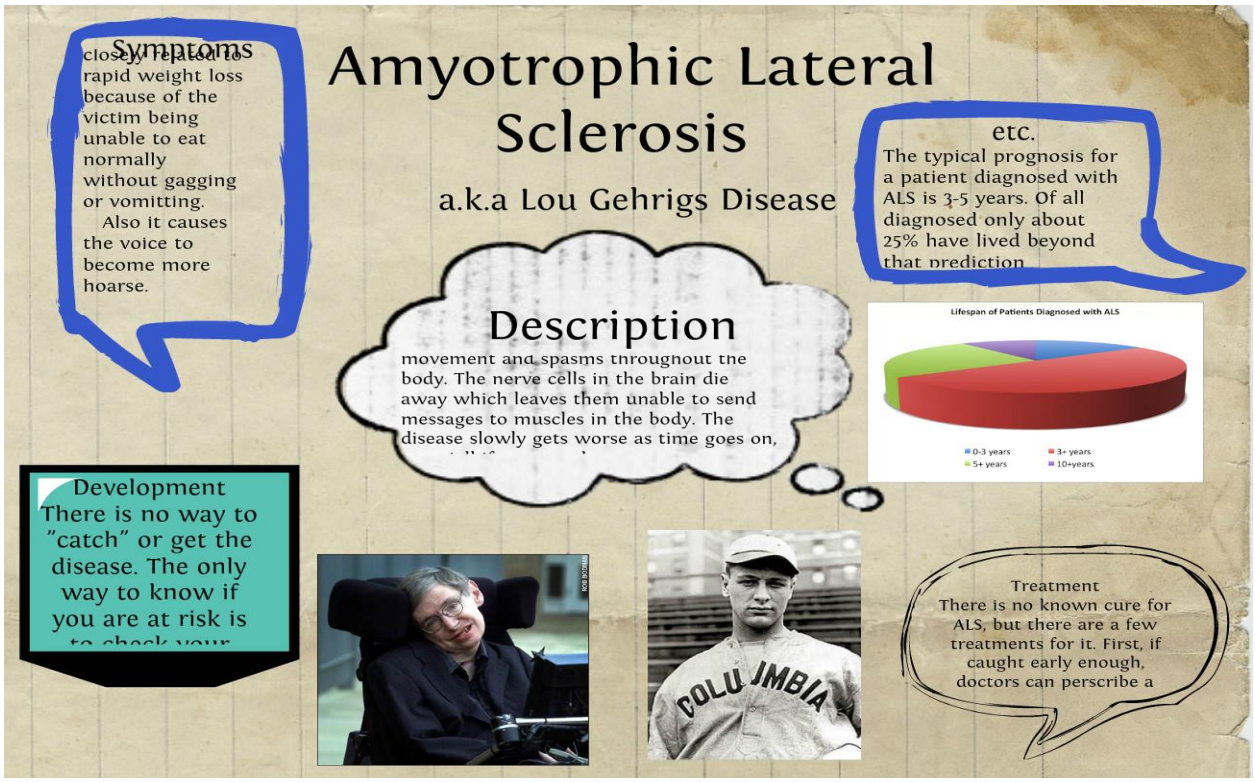
**SYMPTOMS**

Early signs and symptoms of ALS include

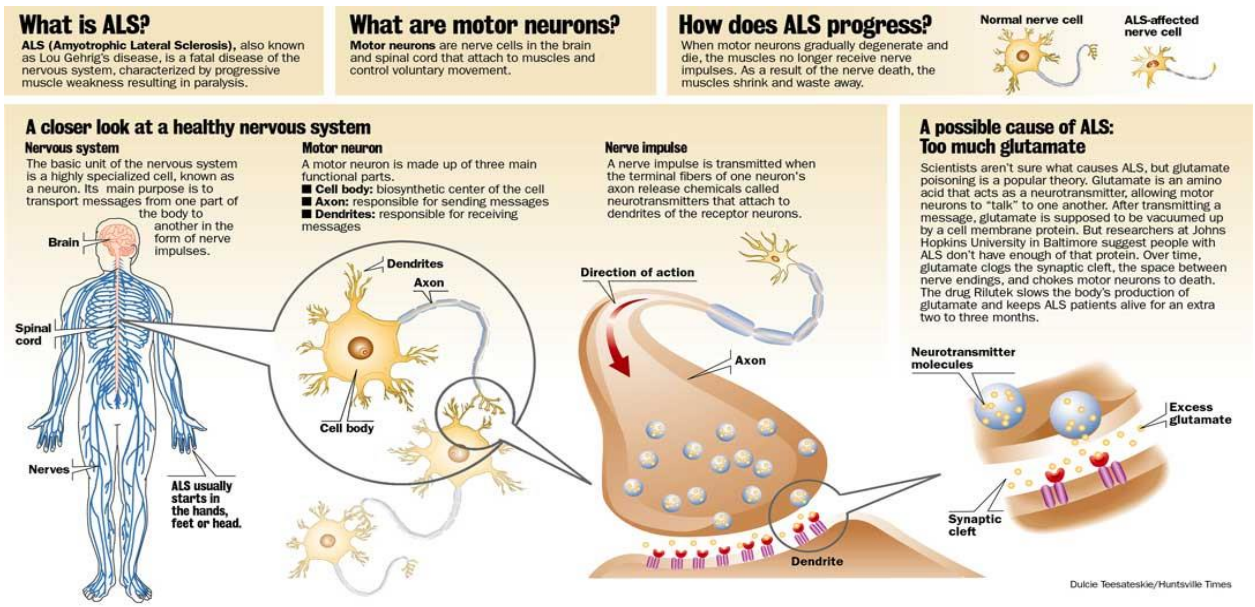
- Difficulty walking, tripping or difficulty doing your normal daily activities
- Weakness in your leg, feet or ankles
- Hand weakness or clumsiness
- Slurring of speech or trouble swallowing
- Muscle cramps and twitching in your arms, shoulders and tongue
- Difficulty holding your head up or keeping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

The disease frequently begins in your hands, feet or limbs, and then spreads to other parts of your body. As the disease advances, your muscles become progressively weaker. This weakness eventually affects chewing, swallowing, speaking and breathing.

However, ALS doesn't usually affect your bowel or bladder control, your senses, or your thinking ability. It's possible to remain actively involved with your family and friends.




Over view of ALS



**Pathogenesis of motor neuron degeneration in ALS**

The exact molecular pathway causing motor neuron degeneration in ALS is unknown, but as with other neurodegenerative diseases, is likely to be a complex interplay between multiple pathogenic cellular mechanisms which may not be mutually exclusive,[25,26] These include:

**1. Genetic factors**

20% of cases with autosomal dominant FALS and 2% of patients with SALS show mutations in the Copper-Zinc superoxide dismutase (SOD1) gene.[27] Mutations in the gene are though to cause disease through a toxic gain of function rather than causing impairment of the antioxidant function of the SOD1 enzyme,[28] Other genes causing familial MND include alsin (ALS2),[29,30] senataxin (ALS4).[31] Vesicle associated membrane protein (VAPB, ALS8),[32] Angiogenin.[33,34] and a mutation in the p150 subunit of dynactin (DCTN1),[35, 36] Recently, mutations in TARDBP gene (encoding the TAR-DNA binding protein TDP-43) located on chromosome 1p36.22 have been linked to familial and sporadic ALS.[37-39] Several other gene mutations have been identified in sporadic cases which may increase susceptibility to ALS, such as mutations in the KSP repeat region in the NEFH gene (encoding neurofilament heavy subunit) , apolipoprotein E ∑4 genotype (APOE) , decreased expression of EAAT2 protein and alterations in the Vascular endothelial growth factor (VEGF) gene to name a few . Excitotoxicity this is the term for neuronal injury induced by excessive glutamate induced stimulation of the postsynaptic glutamate receptors such as cell surface NMDA receptors and AMPA receptors.[40, 41]

**2. Oxidative stress**

Oxidative stress has longed been linked to neurodegeneration and it is known that accumulation of reactive oxygen species (ROS) cause cell death. As mutations in the anti-oxidant enzyme superoxide dismutase 1 (SOD1) gene can cause familial ALS, there is significant interest in this mechanism underlying neurodegenerative process in ALS. This hypothesis is supported by the finding of biochemical changes reflecting free radical damage and abnormal free radical metabolism in CSF and post mortem tissue samples of ALS patients.[42-45] In addition, fibroblasts cultured from ALS patients shows increased sensitivity to oxidative damage controls.[46]

**3. Mitochondrial dysfunction**

Abnormalities in mitochondrial morphology and biochemistry have been reported in sporadic ALS patients, SOD1 transgenic mice and cellular models.[47-53]

### 4. Impaired axonal transport

Motor neuron axons may reach up to one meter in length in humans, and rely on efficient intracellular transport systems. These systems consist of anterograde (slow and fast) and retrograde transport systems, and rely on molecular 'motors', the kinesin complex of proteins (for anterograde) and the dynein-dynactin complex (for retrograde).[54] SOD1 transgenic mouse models of ALS show evidence of slowed anterograde transport and retrograde transport,[55-58] Although no such findings have been observed in humans with ALS, mutations in the kinesin genes are known to cause neurodegenerative motor nerve diseases in humans such as hereditary spastic paraplegia and Type 2A Charcot-Marie-Tooth disease.

## DIAGNOSIS

Differential Diagnoses of ALS: (**BOX-1)**

**Hereditary conditions ■**

■ Spinobulbar muscular atrophy (Kennedy disease)

■ Hereditary spastic par paresis

■ Acid maltase deficiency

■ Facioscapulohumeral muscular dystrophy

■ Adrenomyeloneuropathy

■ Huntington disease

■ Hexosaminidase deficiency

**Metabolic conditions and toxic effects**

■ Hyperthyroidism

■ Hyperparathyroidism

■ Heavy metal intoxication

■ Lathyrism

■ Organophosphate toxic effects

**Immune and/or inflammatory conditions**

■ multifocal motor neuropathy with conduction block

■ Chronic inflammatory demyelinating polyneuropathy

■ Myasthenia gravis

■ Inclusion body myositis

■ Polymyositis

■ Multiple sclerosis

- Paraneoplastic disorders

**Structural disorders**

- Cervical spondylotic myelopathy
- Syringomyelia or syringobulbia
- Postirradiation myelopathy and/or plexopathy
- Tumor
- Cerebrovascular disease

**Other neurodegenerative diseases**

- Corticobasal degeneration
- Multiple system atrophy
- Progressive supranuclear palsy
- Parkinson disease
- Huntington disease

**Other motor neuron diseases**

- Primary lateral sclerosis
- Progressive muscular atrophy
- Spinal muscular atrophy
- Post-polio spinal muscle atrophy
- Benign fasciculation syndrome
- Hirayama disease

**Essential Investigations in Patients with ALS: (BOX-2)**

**Blood tests**

- Erythrocyte sedimentation rate
- C-reactive protein
- Hematological screen: full blood count
- Liver function tests: alanine transaminase and aspartate transaminase levels
- Creatine kinase
- Creatine
- Electrolytes: $Na^+$, $K^+$, $Cl^-$, $Ca^{2+}$, $PO_4$
- Glucose
- Lactate dehydrogenase

■ Thyroid function tests: free tri-iodothyronine, free thyroxine and thyroid stimulating hormone

■ Vitamins: B12, folate

■ Serum protein electrophoresis

■ Serum immunoelectrophoresis

■ β-hexosaminidase subunits α and β assay (where clinically indicated)

■ Ganglioside GM-1 antibodies (where clinically indicated)

■ Serum Borrelia titers and HIV tests (where clinically indicated)

■ Celiac serology (where clinically indicated) Cerebrospinal fluid tests

■ Cell count

■ Protein

■ Glucose

■ Oligoclonal bands (where clinically indicated) Neurophysiology

■ Nerve conduction velocities

■ Sensory and motor amplitudes

■ Presence of focal motor conduction block

**Cerebrospinal fluid tests**

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**Neurophysiology**

■ Nerve conduction velocities

■ Sensory and motor amplitudes

■ Presence of focal motor conduction block

■ Features of denervation on electromyography

■ Motor unit morphology.

**Diagnostic tests**

No definitive diagnostic test for ALS exists. The combination of suggestive clinical signs with negative labo ratory tests and imaging studies for other pathologies supports the diagnosis, although disease progression is a prerequisite.

**Laboratory investigations**

Routine investigation of a patient with apparently typical ALS should include measurement of erythrocyte sedimentation rate, serum and urine protein electro phrases, thyroid function tests, serum calcium and phosphate measurements, and cerebrospinal fluid analysis (Box 2).A heavy metal screen should be performed in individuals with a potential history of exposure. β-hexosaminidase deficiency (Tay–Sachs disease) is common in some ethnic groups, and can mimic ALS. β-hexosaminidase subunits α and β activity should be tested in patients of Ashkenazi Jewish extraction.

**Electrodiagnostic studies**

Electrodiagnostic studies are the most critical ancillary tool in the investigation of ALS. Electromyography can identify loss of lower motor neurons, the hallmark of ALS, and is particularly useful in clinically unaffected regions . The most frequently recognized abhor militias observed on electromyography are fasciculation, spontaneous enervation discharges (fibrillation potentials and positive sharp waves) indicative of ongoing motor neuron loss, and polyphasic units indicative of reinnervation.Fibrillation potentials and positive sharp waves might not develop until one-third of the motor Diagnostic tests No definitive diagnostic test for ALS exists. The combination of suggestive clinical signs with negative laboratory tests and imaging studies for other pathologies supports the diagnosis, although disease progression is a prerequisite.

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**TREATMENT**

**MEDICATION**

Although there is no known cure for ALS, the drug riluzole has been approved for treatment and may slow progression of the disease. It is expensive, however, and appears modestly effective. Generally, treatment is designed to help control symptoms.

Medications prescribed include

- Drugs such as baclofen or diazepam may help control spasticity.
- Gabapentin may be prescribed to help control pain.
- Trihexyphenidyl or amitriptyline may help patients swallow saliva.

The drug riluzole (Rilutek) is the only medication approved by the Food and Drug Administration for ALS. The drug appears to slow the disease's progression in some people, perhaps by reducing levels of a chemical messenger in the brain (glutamate) that's often present in higher levels in people with ALS.

Riluzole may cause side effects such as dizziness, gastrointestinal conditions and liver function changes.

Your doctor may also prescribe medications to provide relief from other symptoms, including:

- Muscle cramps and spasms
- Spasticity
- Constipation
- Fatigue
- Excessive salivation
- Excessive phlegm
- Pain
- Depression
- Sleep problems
- Uncontrolled outbursts of laughing or crying

**THERAPHY**

- **Breathing care**

Over time, you'll have more difficulty breathing as your muscles become weaker. Doctors may test your breathing regularly and provide you with devices to assist your breathing at night.

In some cases, you may choose to breathe through mechanical ventilation. Doctors insert a tube in a surgically created hole at the front of your neck leading to your windpipe (tracheostomy), and the tube is connected to a respirator.

- **Physical therapy**

A physical therapist can address pain, walking, mobility, bracing and equipment needs that help maintain your independence. Some measures include low-impact, exercises to maintain your cardiovascular fitness, muscle strength and range of motion for as long as possible.

A physical therapist can also help you become accustomed to a brace, walker or wheelchair and may be able to suggest devices such as ramps that make it easier for you to get around.

Regular exercise can also help improve your sense of well-being Appropriate stretching can help prevent pain and help your muscles function at their best.

- **Speech therapy**

Because ALS affects the muscles you use to speak, communication becomes an issue as the disease progresses. A speech therapist can teach you adaptive techniques to make your speech more clearly understood. Speech therapists can also help you explore other methods of communication, such as an alphabet board or simple pen and paper.

Later in disease progression, a speech therapist can recommend devices such as tablet computers with text to speech applications or computer based equipment with synthesized speech that may help you communicate. Ask your therapist about the possibility of borrowing or renting these devices.

- **Nutritional support**

Your team will work with you and your family members to ensure you're eating foods that are easier to swallow and meet your nutritional needs. You may eventually need a feeding tube.

- **Psychological and social support**

Your team may include a social worker to help with financial issues, insurance, and getting equipment and paying for devices you may need. Psychologists, social workers and others may provide emotional support for you and your family.

## CONCLUSION

Riluzole is the only drug proven to modify the course of ALS, but this treatment achieves only a modest improve- ment in survival.98 Symptom control and preservation of quality of life remain the cornerstones of management for patients with ALS. Advances in our understanding of ALS have reignited research interest in this clinically heterogeneous disorder. Despite the complexity of the disease, very real improvements have been made in our understanding of the pathophysiology of ALS that will undoubtedly translate into tangible clinical benefits. For example, new research clearly shows that the duration of survival for patients with ALS is determined by many factors, including the clinical phenotype, rate of disease progression, nutritional status and its specialized management, and the specialized management of respiratory failure. Further improvements in survival will depend on advancements in the understanding of the origins and progression of this disease. In the meantime, an urgent need remains for the identification of early biomarkers of disease onset and progression, and efficient approaches to early-phase clinical trials are required to accelerate the identification and development of useful therapies for ALS.

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