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Review Article

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## Amyotrophic Lateral Sclerosis - A Review

Ramesh Dhani, M. Gobinath, C. Yamini\*, Sonalika Patro, G. Divya, T. Lavanya

Ratnam Institute of Pharmacy, Pidathapolur, SPSR Nellore, Andhra Pradesh, India

### ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease. It is characterised by degeneration of motor neurones in the primary motor cortex, cortico-spinal tracts, brainstem and spinal cord by progressive muscular paralysis. Western Pacific people are more prone to this disease. 60 years is the mean age for the onset of sporadic ALS. The symptoms that are present is related to focal muscle weakness and wasting, symptoms may start either distally or proximally in the upper and lower limbs. Paralysis is progressive and due to respiratory failure it leads to death within 2–3 years for bulbar onset cases. The diagnosis is based on clinical history, examination, electromyography, and exclusion of 'ALS-mimics' spondylotic myelopathies, multifocal motor neuropathy, and Kennedy's disease by appropriate investigations.

**Keywords:** Neurodegenerative disease, gene mutation, muscle atrophy, electromyography.

### ARTICLE INFO

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#### \*Corresponding Author

C. Yamini  
Ratnam Institute of Pharmacy,  
Pidathapolur, SPSR Nellore, A.P, India  
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### 1. Introduction

Amyotrophic lateral sclerosis also known as Lou Gehrig's disease or Charcot disease. It is a specific disorder that involves the death of neurons. The term motor neurone disease (MND) is commonly used in United Kingdom. About 90% to 95% of case the causes are not known. About

5–10% of cases are inherited from the heredity. About half of these genetic cases are due to one of two specific genes. It finally results in the death of the neurons that control voluntary muscles. The average survival is three to four years from the onset of the disease about 10% survive

longer than 10 years. This mainly effect respiratory system so most of them die due to respiratory failure. Globally the rates of ALS are unknown. This disease affects about 2 people per 100,000 per year in western countries. In 1824, Charles bell gives descriptions about this disease. Jean-Martin Charcot in 1869 described the connection between the symptoms and the underlying neurological problems in the disease.

## 2. Signs and Symptoms

The foremost symptoms of ALS

- Muscle weakness
- Muscle atrophy
- Difficult in swallowing, breathing, cramping
- Stiffness of affected muscles
- Slurred and nasal speech

The early symptoms of ALS are the damage of motor neurons in the body.

### Initial symptoms:

About 75% of people the first experience is the weakness or atrophy in an arm or leg and this disorder is known as "limb-onset" ALS. When walking or running or even stumbling may be experienced and often this is marked by walking with a "dropped foot" which drags gently on the ground. About 25% of cases begin as progressive bulbar palsy termed "bulbar-onset" ALS. Initial symptoms include difficulty in speaking, swallowing, and eventually breathing.

### Progression:

As the order and rate of symptoms varies from person to person. Eventually most of the people are enable to walk by using their limbs. They also lose the ability to speak and swallow food, where most of the people end up on a portable ventilator, called BIPAP. The rate of progression can be measured using a measure called the "ALS Functional Rating Scale Revised (ALSFRS-R)".

**Advanced stages:** After the onset of the symptoms within three to five years most of the people die due to the respiratory failure. The survival time from onset to death is around 39 months, and about 4% survive longer than 10 years. Difficulty in chewing and swallowing makes eating very difficult and increases more risk of choking or aspirating food into the lungs. Aspirating pneumonia can develop in advanced stages there by maintaining a healthy weight becomes a significant problem, which may require the insertion of a feeding tube. As the diaphragm and inter costal muscles of the rib cage becomes weaken there is a difficulty in respiration. In late stages, the oculomotor nerve that controls the movements of the eye can be affected as can the extra ocular muscles (EOMs). The eye movements remain unaffected largely until the later stages due to differences in the extra ocular muscles compared to the skeletal muscles that are initially. The person's condition may resemble locked-in syndrome in the advanced stages of the disease.

### Causes

**Genetics:** About 5–10% of cases are hereditary. Superoxide dismutase is a enzyme and also powerful anti-oxidant that protects the damage caused by superoxide

a toxic free radicals that is generated in mitochondria .During normal metabolism free radicals are highly reactive molecules produced by cells. They cause damage to DNA and proteins within cell due to accumulation. The superoxide radicals are not neutralized due to the mutation in SOD1, This mutation is expected to be transmitted in an autosomal dominant manner, and has a hundred different forms of mutation. The mutant SOD1 gene induces ALS causing mutation. D90AOD1 is the most common mutation found in Scandinavian countries, and people with this form of the disorder survive for an average of 11 years. In 2011, a genetic abnormality known as a hexa nucleotide which is associated with ALS combined with frontal-temporal dementia ALS-FTD. The gene is also found in people of Filipino descent.

### SOD1:

In 1993, scientists discovered that mutations in the gene that produces the Cu-Zn superoxide dismutase (SOD1). This enzyme is a powerful antioxidant that protects the body from damage caused by superoxide, a toxic free radical generated in the mitochondria. Free radicals are highly reactive molecules produced by cells during normal metabolism. This cause damage to DNA and proteins within cells due to accumulation. 110 different mutations in SOD1 have been linked with the disorder, some of which (such as H46R) have a very long clinical course, while others, such as A4V, is exceptionally aggressive., Programmed cell death (apoptosis) is up regulated When the defences against oxidative stress fail occurs.

### ALS2/ALSIN

It is a rare, autosomal recessive, juvenile onset disease. ALS2 is mainly characterized by limb and facial spasticity, spastic dysarthria, uncontrolled laughter, subsequent lower motor neuron signs and bladder dysfunction. The locus of ALS2 is mapped to chromosome 2q33-2q35 via linkage analysis in large Tunisian kindred. Premature stop codon due to the deletion mutations. Alsin is alternatively joint together to produce a long and a short transcript.

### ALS4/senataxin (SETX):

ALS4 is a rare, juvenile onset, autosomal disease. ALS4 is characterized by distal limb weakness, muscle atrophy, and pyramidal sigs. Bulbar and respiratory muscles are spared. ALS progression is slow and the patients usually have a normal life span. Senataxin is linked to chromosome 9q3 and sequencing 19 genes in this locus shows 3 distinct missense mutations in the SETX gene in 3 families with ALS.

### Other factors:

There is no family history for these the disease. head trauma, military service, frequent drug use, and participation in contact sports in 90% of cases. Other causes includes on the role of glutamate in motor neuron degeneration. Glutamate is one of the neurotransmitters in the brain. Scientists are described that glutamate levels in serum and spinal fluid is higher levels in people with ALS as compared with healthy people. Riluzole is the only one drug. It is approved by food and drug administration. Riluzole is targets glutamate transporters. It only has a

modern effect on survival, But not suggesting that excess glutamate is not the sole cause of the disease.

### 3. Pathophysiology

Amyotrophic Lateral sclerosis is the death of both upper and lower motor neurons in the motor cortex of the brain, the brain stem, and the spinal cord. Destruction of both upper and lower motor neurons are develop protein-rich inclusions in their cell bodies and axons. This occurs due to defects in protein degradation. These inclusions contain ubiquitin, and also ALS-associated proteins. These are SOD1, TAR DNA binding protein (TDP-43, the American physician william Welch trained in German pathology and also including under Cohnheim, and In 1878 he is opened America's first scientific laboratory and pathology laboratory at Bellevue Hospital in New York City. Welch's course drew enrolment from students at other medical schools, which is responded by opening their own pathology laboratories.

### 4. Diagnosis

There is no specific test for diagnosis of ALS. Although the presence of upper and lower motor neuron single limb. The diagnosis of ALS is primarily based on the a symptoms and signs the physician observes in the person and a series of tests to rule out other diseases. By usually conducting a neurologic examination at regular intervals, Physicians obtain the person's full medical history. Disease symptoms are muscle weakness, atrophy of muscles, hyperreflexia, and spasticity are worsening. Because symptoms of ALS can be similar to other more treatable diseases or disorders, some appropriate tests must be conducted to exclude the possibility of other conditions. One of these tests is electromyography (EMG) it is a special recording technique that detects electrical activity in muscles. Certain EMG findings can support the diagnosis of ALS. Another common test is measures nerve conduction velocity (NCV). If any Specific abnormalities are present in the nerve conduction velocity (NCV) these results that the patient has a form of peripheral neuropathy (damage to peripheral nerves) or myopathy (muscle disease) rather than ALS. And also a magnetic resonance imaging (MRI) is often normal in people with ALS, they can reveal evidence of ALS.

**Diagnostic tests:** No specific diagnostic test for ALS exists. The combination of clinical signs with negative laboratory tests and imaging studies are supports the diagnosis and progression of the disease.

#### Laboratory investigations:

Routine investigation are done patient with typical ALS should include measurement of

- Erythrocyte sedimentation rate
- Serum and urine protein electrophoresis
- Thyroid function tests
- Serum calcium and phosphate measurements, and
- Cerebrospinal fluid analysis.

A heavy metal screen is also performed in individuals with a potential history of ALS. In some groups -hexosaminidase deficiency (Tay-Sachs disease) is common and ALS. In patients with Ashkenazi Jewish

extraction -hexosaminidase subunits and activity should be tested.

#### Electro-diagnostic studies:

For investigation of ALS Electro-diagnostic studies are the most important. Electromyography can identify loss of lower motor neurons and is particularly useful in clinically unaffected regions in brain. The most frequently recognized abnormalities observed on electromyography are fasciculation, spontaneous denervation discharges (fibrillation potentials and positive sharp waves) indicative of ongoing motor neuron loss, and polyphasic units indicative of re innervation. Fibrillation potentials and positive sharp waves might not develop until one-third of the motor neurons have been lost, although their presence in clinically normal muscle tissue may facilitate an early diagnosis. Transcranial magnetic stimulation is may help in the identification of patients with subclinical upper motor neuron dysfunction. Short-interval and long-interval intracortical inhibition and peristimulus time histograms is the useful in the diagnosis of ALS pathophysiology, but these are not used routinely in clinical settings.

**Genetic testing:** A systematic review of all familial ALS cases suggests that up to 5% of cases follow a Mendelian pattern of inheritance. In familial ALS contain total of 15 genes and loci have been identified in The clinical and pathological presentation. It is very similar to that of sporadic cases. accurate diagnosis of familial cases of ALS can be challenging, as the lifetime risk of developing the disease is 1:400. The size of a given extended and the living risk for developing ALS can be calculated. For any index case with a similar to 17 first-degree and second-degree relatives, there is a 5% chance to develop a second member of the Relatively somebody by blood, will also develop sporadic ALS. Mendelian pattern of inheritance of the disease is greatly increased when three affected members of blood relatives have been identified. In 68 genes only 15 genes are responsible for known to be associated with ALS. Mutations occurred genes such as SOD1, TARDBP, ANG, VCP and FUS are associated with typical ALS; the remaining genes are associated with unusual phenotypes. Specific selection of patients with familial ALS for mutations in these known genes might offer some benefit, as preliminary information from mouse studies suggests that passive immunization strategies can reduce severity of disease progression in the SOD1 model. There is a 69 Clinical trials using antisense drugs, 70 arimoclomol (phase II-III trials) and 72 pyrimethamine (phase I-II trials) have commenced. However, genetic screening of unaffected members of ALS blood relatives is currently of little utility, as known mutations have limited penetrance. The risk of disease cannot be determined during an asymptomatic carrier.

#### Neuro imaging studies:

In neuroimaging technique contain Magnetic resonance image of the brain and spinal cord is the most useful in ALS. Mainly to prevent syndromes that mimic ALS. In some patients with ALS, rounded foci of high signal intensity are plain along the corticospinal tract and precentral and frontal cortex on T2-weighted, fluid-reduction inversion recovery and proton-density-weighted

MRI sequences. but, these MRI features are not specific for ALS and the presence of upper motor neuron signs, not useful as markers of disease progression. In advanced MRI techniques, containing diffusion tensor imaging, magnetization transfer, and proton magnetic resonance spectroscopy and resting functional MRI. in addition to morphometry—a neuroimaging analysis technique is uses the statistical methods are useful to identify specific ALS-associated pathology in a non invasive manner. At present, for cross-sectional and longitudinal studies of ALS, these techniques are primarily used as research tools, although diffusion tensor imaging, voxel-based morphometry and resting functional MRI have been used in both and have the potential to be developed into sensitive new neuroimaging techniques 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.

## 5. Treatment

**Medications:** Riluzole (Rilutek) only the drug has been used increase the survival by several months, and may have a longer survival benefit for those with a bulbar onset. It also extends the time before a person needs ventilation support. People taking these drug must be monitored for liver damage (occurring in about 10% of people taking the drug) because these drug causes liver damage. Riluzole (Rilutek) is approved by Food and Drug Administration and recommended by the National Institute for Clinical Excellence. Riluzole does not reverse damage already done to motor neurons. Other medications also used for 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, dysphasia, and constipation. Baclofen and diazepam are mostly used to control the spasticity caused by ALS and trihexyphenidyl or amitriptyline may be prescribed when people with ALS begin having trouble swallowing their saliva.

## 6. Management

### Breathing support:

When the muscles that assist in breathing weaken, use of ventilatory assistance are:

1. Intermittent positive pressure ventilation,
2. Bi-level positive airway pressure (BiPAP),
3. Biphasic cuirass ventilation (BCV)

These may be used to aid breathing. These devices artificially inflate the person's lungs from various external sources that are applied directly to the face or body. These devices are useful for maintain oxygen and carbon dioxide levels, in muscles for longer time. BCV has the major advantage of being able to maintain in clearing secretions by using high-frequency oscillations followed by several positive expiratory breaths. People may eventually prefer these forms of mechanical ventilation (respirators) in which a machine inflates and deflates the lungs. To be more 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 tracheotomy, in which a plastic breathing tube is inserted directly in the person's windpipe through an opening in the neck.

External ventilation machines such as BiPAP are frequently used to support breathing, initially at night, and later during the daytime, also as well. The use of BiPAP (more called as non invasive ventilation, NIV) is only a temporary remedy, however, and long before BPAP is not effective, persons should decide whether to have a tracheotomy and long-term mechanical ventilation. At this point, some persons choose palliative hospice care.

### Therapy:

Physical therapy plays a large key role in rehabilitation for individuals with ALS. Specifically, physical and occupational therapists can set goals and promote benefits for individuals with ALS by maintaining delaying loss of strength, maintaining endurance, limitation of 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. 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. Physical therapy includes, 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 are recommended exercises that provide benefits without overwork load to muscles. They can suggest devices such as ramps, braces, walkers, bathroom equipment (shower chairs, toilet risers, etc.), and wheelchairs that help patients remain motility.

### Nutrition

Patients and caregivers can learn from dieticians how to plan and prepare various small meals throughout the day that provide enough calories, fibres, and fluid and how to avoid foods that are difficult to swallow. Patients may begin frequently using suction devices to remove excess fluids or saliva and prevent choking. Occupational therapists shall assist with recommendations for equipment to ease the physical task of self-feeding. Speech-language pathologists make food choice recommendations that are more conducive for their unique deficits and abilities. If patients can no longer get enough nourishment from eating, doctors may advise them for inserting a feeding tube into the stomach. This is used for reducing the risk of choking and pneumonia that can result from inhaling liquids into the lungs by using this feeding tube. The tube is not painfully inserted and does not prevent patients from eating food orally if they wish.

## 7. Conclusion

There is a great heterogeneity for genetic spectrum of f ALS and s ALS. Several genes in ALS are known to cause many other neuro degenerative diseases, such as also in

with PLS and infantile onset ascending hereditary spastic paralysis (IAHSP), The genes responsible for these diseases are Senataxin with SCAR1 or AOA2, spatacsin with HSP, VAPB with SMA, FIG 4 with CMT type 4 J, OPTN. By the advanced genetic technology, we can expect the number of genes involved in fALS as well as sALS will be to increase. In addition, the utilization of transgenic animal models may provide useful tool to study the pathogenesis of ALS. Emphasis should also be made on elaborating the gene-environment interactions and crosslink in ALS, as 90% of cases are sporadic in origin, which may help better understand the nature of the disease. It is difficult to predict the future outcome in ALS, but the researchers identification of novel genes, gene modifiers and the different molecular pathways caused by the aberrant genes, might advance our research in this area. Hopefully, the use of the deep sequencing techniques, transgenic animal models, retrograde studies on available data and prospective design of future studies, may help broaden our vision in understanding the ALS genetics and pathogenesis. Strategic approach based on new ALS genes and drug trials on animal models should enable us to uncover new treatment modal.

promptly promote the sustained development of a system of medical care for and research into rare diseases.". *Intractable & rare diseases research* 3 (3): 94–6.

[10] Dugdale DC, Hoch DB, Zieve D (27 August 2010). "Amyotrophic lateral sclerosis". *A.D.A.M. Medical Encyclopedia*.

## 8. References

- [1] Sabatelli M, Madia F, Conte A, Luigetti M, Zollino M, Mancuso I, Lo Monaco M, Lippi G, Tonali P (16 September 2008). "Natural history of young-adult amyotrophic lateral sclerosis". *Neurology*
- [2] Kelly, Evelyn B. (2013). *Encyclopedia of human genetics and disease*. Santa Barbara, Calif.: Greenwood.
- [3] Ellison, edited by Seth Love, David N. Louis, David W. (2008). *Greenfield's neuropathology* (8th ed. ed.). London: Hodder Arnold. p. 947. "Motor Neuron Diseases Fact Sheet: National Institute of Neurological Disorders and Stroke (NINDS)". Retrieved 7 November 2010.
- [4] Kiernan, MC; Vucic, S; Cheah, BC; Turner, MR; Eisen, A; Hardiman, O; Burrell, JR; Zoing, MC (12 March 2011). "Amyotrophic lateral sclerosis". *Lancet* 377 (9769): 942–55.
- [5] Miller, RG; Mitchell, JD; Moore, DH (14 March 2012). "Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)." *The Cochrane database of systematic reviews* 3
- [6] Malamut, edited by Joseph I. Sirven, Barbara L. (2008). *Clinical neurology of the older adult* (2nd ed. ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 421.
- [7] Byrne, S. et al. Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis. *J. Neurol. Neurosurg. Psychiatry* 82, 623–627 (2011).
- [8] Youngson, David B. Jacoby, Robert M. (2004). *Encyclopedia of family health* (3<sup>rd</sup> ed.). Tarrytown, NY: Marshall Cavendish. p. 1256.
- [9] Song, P (August 2014). "The Ice Bucket Challenge: The public sector should get ready to