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# Amyotrophic lateral sclerosis- A review

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## ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease, rapidly progressive, invariably fatal motor neuron disease attacking neurons controlling voluntary muscles. It is characterized by muscular paralysis reflecting degeneration of motor neurons in brain stem, corticospinal tract, primary motor cortex and spinal cord. Most ALS cases are sporadic but few (5-10%) cases are familial. The cause is not known in 90-95% cases and about 5-10% cases are genetically inherited. The mean age of onset of sporadic ALS is 60 years. Overall studies suggest that males are affected more than females. Prevalence and incidence of ALS is relatively uniform. Approximately 2/3$^{rd}$ of patients with typical ALS have spinal form (limb onset) and present symptoms related to focal muscle wasting and weakness. Gradually spasticity may develop in weakened limbs, affecting gait mainly. Patients with bulbar onset ALS present usually limbs symptoms, dysphagia for solids and liquids, dysarthria symptoms may develop simultaneously with bulbar symptoms and in majority of cases it occur within 1-2 years. ALS is diagnosed on the basis of clinical history, physical examination, skin biopsy, lumbar puncture. The main pathological feature comprise loss of motor neuron with interneuron- ubiquitin, TDP-43 immunoreactive inclusions in degenerating lower neurons. The management of ALS include symptomatic treatment, ventilatory support and nutritional management. Non- invasive ventilation improves survival rate and quality of life. Till date Riluzole is the only drug that has shown to lengthen survival of the patients.

**Keywords:** Neurodegenerative disease, (ALS) Amyotrophic lateral sclerosis, Dysarthria, Ubiquitin, Riluzole.

## INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is termed as Charcot's disease after the French scientist named Jean Martin Charcot who described it for the first time around 1869. It is also termed as Lou Gehrig's disease after New York baseball player was affected with ALS. In Europe, ALS is referred to as MOTOR NEURON DISEASE where the cells which are affected are described here. There is no successful treatment available for ALS. Although many descriptions for around past 150 years with a significant knowledge of its pathology it remains an ill-defined terminal disease. [1]

## DEFINITION

Amyotrophic lateral sclerosis (ALS) is usually characterized by progressive degeneration of motor

neurons and it is also called as neurodegenerative syndrome. It paralyzes the motor neurons commonly in primary motor cortex, brain stem and spinal cord. Amyotrophic= Muscular atrophy, Lateral sclerosis= Scarring of anterior and lateral corticospinal tracts. It attacks the nerve cells that are used in voluntary muscle actions. The ability of brain to control voluntary movement is lost. It generally begins with twitching of muscle and weakness in arm or leg. It also affects the ability to control the muscles which are needed to move, speak, eat and breathe. This disease can't be cured but managed with disease modifying and symptomatic treatment. [1, 2]

## CLASSIFICATION

- Classical ALS (Sporadic ALS) - It is most common form of ALS which can affect anyone. It is progressive deterioration of both upper motor neuron and lower motor neuron.
- Primary ALS- It is a rare form of ALS. It is progressive neurological disease characterized by deterioration of upper motor neuron. Generally lower motor neurons are not affected.
- Progressive muscular atrophy (PMA) - It is neurological disease characterized by deterioration of lower motor neurons. Generally upper motor neurons are not affected.
- Progressive bulbar palsy (PBP) – It is a condition which initiates with lower motor neuron deterioration resulting in difficulty associated with speaking, chewing and swallowing.
- Familial ALS (FALS) – It is progressive neurological disease due to genetic mutation affecting more than a member of same family.[3]

## EPIDEMIOLOGY

- Although ALS is a rare condition but the social and economic burden has considerable importance.
- The risk of sporadic amyotrophic lateral sclerosis is estimated to be 1 in 1000 but with more accurate it is about 1 in 400 by the age of 70.
- Slight males are more likely to be affected than females due to hormonal factors in women where men's are likely being exposed risk factors.
- People aged above 50 years are mostly affected.
- Though , onset of ALS can occur from teenage to late 80's,
  -Mean age of onset of Sporadic ALS (SALS) is 65 years
  -Mean age of onset of Familial ALS (FALS) is 46-55 years.
- One of the highest rate of ALS in the world is seen in Finland due to genetic reasons.[4,5,6]

## CLINICAL FEATURES

Amyotrophic Lateral Sclerosis (ALS) begins in the limbs for about two-third of the patients where the first symptoms includes unilateral and focal with early findings like peroneal nerve injury, dysbasia, hand weakness or difficulty in lifting the arms. Patients generally notice muscle twitch or cramps which leads to onset of weakness over months or years. During advanced stages patient develops flexor spasms. These are the involuntary spasms which occurs due to excess activation of flexor arc in spastic limb. Some other symptoms include sensory symptoms, cognitive symptoms, urgency of micturition…etc. Patients who suffers with bulbar onset ALS after ingestion of little amount of alcohol presents with the symptom like dysarthria of speech, dysphagia for solids or liquids. The initial onset of ALS begins with several patterns where about 70% have spinal onset affecting limbs. Cervical subset results in muscle weakness in upper limbs whereas lumbar subset arises in lower limbs. Some of the patients have bulbar onset where muscles of face and neck are affected which is more common in women and elderly patients. Many other rare onsets are seen such as respiratory onset where muscles of respiratory systems are affected. [7]

## DIAGNOSIS

There is no test available to provide a definitive diagnosis of early ALS. The diagnosis of ALS is primarily based on signs and symptoms. In addition to that a number of tests are conducted usually to rule out other similar conditions (ALS mimic syndromes). Usually ALS mimic syndromes does not rapidly progresses and the patients also survive for longer life. [5, 6]. Different diagnostic criteria are available for the diagnosis of ALS, namely El Escorial criteria revised and Lambert criteria, which are not useful in early diagnosis. [4]

- **Up on physical examination**

- Muscle spasms, tremors, twitching
- Tongue twitching (common)
- Clumsy of stiff walking

- Loss of gag reflex
- Weakness mainly in one area
- Abnormal reflexes
- Increased reflexes at joint
- Emotional incontinence.[6]

**Electromyography**

- The hallmark symptom of ALS, loss of lower motor neuron (LMN) can be diagnosed by Concentric Needle EMG study. The commonly observed abnormalities in EMG are rapid denervation charges, fasciculation's which indicates loss of neurons/ LMN dysfunction.[5]
- Muscle / Nerve biopsy: It is rarely needed but it is considered if ALS presentation is atypical. The compatible histological findings are –
  - Presence of necrotic muscle fibers
  - Fiber type grouping
  - Presence of small, angular fibers (denervation)
  - Scattered hypertrophied muscle fibers. [4, 6]
- MRI/ CT scanning: The main purpose of neuroimaging in the diagnosis of ALS is to exclude the treatable structural lesions that mimics ALS (Ex. Multiple sclerosis, tumors, spinal radiculopathy). Result of these scanning is generally normal in patients with ALS.[4,6]
- Other Laboratory Tests: These are some of the laboratory tests that may be abnormal in atypical case of ALS. These include
  -Spinal tap/lumbar puncture (elevated CSF protein)
  -Serum creatinine (because of loss of skeletal muscle mass)
  -Increased bicarbonate levels (hypochloremia (in advanced respiratory compromise)
  -Muscle enzymes such as serum creatinine kinase
  -Thyroid and Antithyroid hormone levels
  -Urine analysis for heavy metals
  -Serum protein electrophoresis. [4, 6]

## DIFFERENTIAL DIAGNOSIS

ALS is many times misdiagnosed to ALS –mimic syndromes which have a similar clinical feature and presentation to ALS. [4, 5]

They are

- Kennedy's disease( spinobulbar muscular atrophy)
- Multifocal motor neuropathy(MFMN)
- Myokymia syndrome
- Inclusion body myositis
- Lumbo sacral radiculopathy
- Syringomyelia
- Cerebral lesions
- Skull bone lesions cervical spondylotic myelopathy
- Primary lateral sclerosis
- Lyme disease
- Neuro sarcoidosis
- Spinal muscular atrophy
- Myasthenia gravis
- Huntington's disease
- Hexosaminidase deficiency
- Progressive supranuclear palsy.

## ETIOLOGY

In ALS, the nerve cells that control the movement of our muscles die gradually, thereby muscles progressively weaken and begin to waste away .research studies says that ALS, is inherited in 5-10% of cases. The disease is classed as autosomal dominant in these patients.90-95% of ALS is sporadic means it occurs without a family history. [2]. The following are the possible causes of ALS: [8]

### Gene mutation

Genetic mutations are one of the most likely causative agents of inherited ALS. It appears almost identical to non-inherited form. Mutations in the gene for enzyme superoxide dismutase 1(SOD-1) or copper zinc SOD have been found in 15-20 %. Mutations for gene TARBDP- Tran's active response DNA –binding protein of 43 KD accounts for about 5% of familial ALS cases. ALS is associated with several other genetic mutations in genes coding for different proteins like fused in sarcoma (FUS) and valosin containing protein (VCP). Recently, a genetic defect was observed with an expansion of non-coding hexanucleotide GGGGCC which repeat in the chromosome 9, open reading frame 72(C90RF72).

### Chemical imbalances (glutamate toxicity)

Glutamate is a chemical messenger present in the brain, around the nerve cells in the spinal fluid. In patients with ALS, this chemical gradually increases in its levels. Thus it becomes toxic to some nerve cells.

### Disorganized immune system

In an auto immune disorder, immune system begins to attack some of the body's normal cells, thus leading to death of neurons. Microglia, the immunologic cells in nervous system can be beneficial and harmful in ALS. They may be protective up to a certain point and then become damaging.

### Protein mishandling

Normal protein configuration is very essential for normal functioning of nerve cells. Mishandled proteins with in the neurons may lead to gradual accumulation of proteins eventually causing death of nerve cells.

### Oxidative stress

It is a phenomenon that occurs when there is an imbalance between the production of oxygen containing molecules that contain electrical charge that can be toxic and a biological systems ability to readily detoxify them.

### Mitochondrial dysfunction

Mitochondria are microscopic energy factories present inside the cell. They have their own DNA. Mitochondrial abnormalities may be involved in ALS progression. [8]

## Pathogenesis

ALS is characterized by both upper motor neuron (corticospinal motor neurons) degeneration. It involves death of these neurons as well as reactive gliosis, replacing these dead neurons. [9]

The exact molecular pathway of motor neuro degeneration is not known, the following are thought to play a major role in pathology of ALS. They are: [4]

- Inclusion bodies
- Oxidative stress
- Excitotoxicity
- Mitochondrial abnormalities
- Axonal transport abnormalities
- Growth factors
- RNA metabolism disorders
- Apoptosis
- Genetic factors.

### Inclusion bodies

The hallmark of LMN (lower motor neuron) pathology of ALS is the presence of intracellular inclusion bodies in neuronal soma, proximal dendrites as well as glia. Ubiquitylated inclusions (UBI): UBI are found in 100% sporadic ALS cases. These are the specific inclusions common in both FALS and SALS types, in cortical frontal and temporal lobe neurons Tar -DNA binding protein 43(TDP-43) and fused sarcoma protein (FUS) are the components of ubiquinated inclusions in SALS. The complete composition of UBI remains unclear but several other proteins were analyzed in UBI such as ubiquitin, cu/Zn SOD 1 and dorfin. [9] Bunina bodies: These are eosinophilic para crystalline bodies present in LMNs of many ALS cases. They are immune reactive for a cysteine protease inhibitor called cystatin C. [10] Hyaline conglomerate inclusions (HCI): these are found in motor cortex neurons. They consists of intracellular inclusions of peripherin and neurofilaments hyper phosphorylated sub unit.

### Oxidative stress

The accumulation of reactive oxygen species (ROS) leads to death of the cell. Any mutation or alteration in anti-oxidant enzyme –superoxide dismutase 1(SOD1) gene can cause familial ALS. Recent studies shows that they may cause 0.7-4% cases of sporadic ALS. The hypothesis of mutant SOD1 neurotoxicity include inhibition of proteasome activity, mitochondrial damage and formation of intra cellular aggregates of SOD1 which is an early event in ALS. This mediates motor neuron degeneration and also seems to disrupt RNA processing in the cell.

### Excitotoxicity

Glutamate excitotoxicity is the dominant hypothesis of pathogenesis of ALS. The main excitatory neurotransmitter identified in mammalian CNS is Glutamate. However in high concentration it is toxic to motor neuron. Defective glutamate transport, results in elevated glutamate levels which have been reported in significant number of patients in sporadic cases. Increased glutamate levels were found in spinal fluid and serum samples of SALS patients. Excess glutamate levels leads to activation of glutamate ionotropic AMPA receptors in neurons and glial cells. AMPA receptor activation triggers

changes in mitochondria such as decreased ATP synthesis, decrease the cellular oxygen consumption, oxidative phosphorylation uncoupling and increase in mitochondria reactive oxygen species (ROS) production, causing apoptosis. Glutamate receptor dysfunction is another possibility of excitotoxicity.

### Mitochondrial abnormalities

Mitochondria of ALS patients show elevated levels of calcium and decreased activity of respiratory chain complexes I and IV, which implicates defective energy metabolism. Mitochondrial abnormalities may be associated with mutations of gene SOD 1. Mutant SOD1 translocate to the inter membrane space and matrix in mitochondria. It is also associated with mitochondrial outer membrane. Its consequences is reduced mitochondrial membrane potential and decreased electron transport chain (ETC) activity. Release of calcium and cytochrome C to the cytosol and simultaneous production of reactive oxygen species (ROS) lead to death of cell in ALS.

### Axonal transport abnormality

Cytoskeleton proteins such as neurofilaments (NF's) give structure and shape to motor neurons and they play a role in axonal anterograde and retrograde transport. Anterograde and retrograde systems rely on kinesin and dynactin complexes respectively.SOD1 ALS patients showed the evidence of slowed anterograde and retrograde transport. Neurodegenerative motor nerve diseases in humans such as type-2A Charcot-Marie-Tooth disease and hereditary spastic paraplegia are due to mutations or alterations in kinesis genes. Mutations in dynactin complex causes a lower motor neuron disorder with vocal cord paresis.

### Growth factors

Several growth factors have been potentially implicated in the pathogenesis of ALS. The most investigated growth factor is the vascular endothelial growth factor (VEGF).this is a protein involved in angiogenesis and vasculogenesis and in oxygen supply restoration up on limited blood circulation. Overproduction of VEGF causes delay in onset and progression of motor neuron diseases. Animal studies shows that VEGF is a neuro protector. VEGF –B, homologue of VEGF which has minimal angiogenetic activity showed protective nature for cultured primary motor neuron. Some other beneficial growth factors are neurotropic factors derived from glial cells, InsulinGF-1 and some other neurotropic factors.

### RNA metabolism disorder

DNA binding protein of 43 KDa (TDP-43) which is encoded by TARBDP gene present in chromosome – 1 has been analyzed in motor neuron of patients with SALS. TDP-43 positive inclusions were also found in patients with non SOD1 FALS. TDP-43 is a nuclear protein expressed in almost all the tissues. It binds to mRNA and DNA and regulates splicing, translation and gene transcription processes of mRNA processing. TDP-43 interacts with cytoplasmic ataxin- 2-protein resulting in TDP-43 accumulation in the misfolded aggregates. Formation of these aggregates are known to be implicated in neuronal death.

### Apoptosis

Apoptosis is a programmed cell death which is involved in several physiological processes during development and aging. Inappropriate apoptosis is a potential mechanism involved in ALS and several other neurodegenerative diseases.

### Genetic factors

SOD1 gene mutations are observed in both FALS and in some of SALS cases. Other genes causing familial motor neuron degeneration include alsin, senataxin, vesicle associated membrane protein (VAPB), angiogenin and a mutation in $p^{150}$ sub unit of dynactin (DCTN1). Recently mutations in gene TAR DNA binding protein TDP-43 (TARDBP) located on chromosome 1p [36-22] have been linked to both FALS and SALS. Gene mutations in SALS include mutation in the KSP repeat region in the NEFH gene –encoding neurofilaments heavy sub unit, apolipo protein EΣ4 genotype (APOE), decreased depression of EAAT2 protein and alteration in the vascular endothelial growth factor (VEGF) gene. [11]

## SIGNS AND SYMPTOMS

In about 80 % of patients symptoms begin with limb involvement

- Initial symptoms of patients with upper limb onset includes-
  -dropping of wrist interfering with poor performance.
  -wasting of intrinsic hand muscles.
  -cramping and stiffness of finger.
- Initial symptoms of patients with lower limb onset includes-
  -slapping gait, foot drop.
  -stumbling, tripping.
- Symptoms of patient with bulbar onset includes-
  -aspiration
  -decreased volume of speech
  -slurred speech
  -hoarseness (abnormal voice changes)
- Some special cognitive and emotional difficulties in some ALS patients are
  -depression
  -maladaptive behavior
  -executive function impairment
  -Involuntary crying or laughing.
- Symptoms seen in more advanced disease are
  -muscle cramps
  -muscle atrophy
  -Drooling
  -loss of speech. [6]

## RISK FACTORS

- Age - occurs between 40-60 year's.
- Sex - men's are affected more than women.
- Heredity- in case of FALS patients their children have 50 -50 chance of developing disease.
- Environmental factors such as smoking and occupational lead exposure also increases the risk of ALS.[2]

## COMPLICATIONS

It includes –

- Aspiration pneumonia
- Respiratory insufficiency
- Deep vein thrombosis
- Pulmonary emboli
- Ambulation deterioration
- Frontotemporal dementia
- Decubitus ulcers
- Progressive muscular atrophy
- Acute respiratory distress syndrome
- Pressure sores.[6,12]

## HISTOPATHOLOGICAL FEATURES

The histopathological hallmarks of the ALS are degeneration of motor neurons followed by loss of motor neurons with the presence of intraneuronal inclusions in degenerating neurons and glia.

### Bunina bodies

Small, hyaline intra cytoplasmic inclusions, eosinophilic, which stains positively for cystatin. Bunina bodies are rarely seen in other conditions.

### Hyaline conglomerate inclusion (HCI's)

This type of argyrophilic inclusions are seen in spinal cord motor neurons. These are mainly associated with FALS and rarely seen in SALS. These are also seen in some other neurodegenerative diseases.

### Ubiquitinated inclusions or ubiquitin immunoreactive (UBI's, Ub-IR)

These are skein like inclusions (SLI's) which have filamentous compact spherical bodies. TAR DNA binding protein 43 (TDP-43) is major constituent present in ubiquitin positive inclusions. They can be seen in up to 95% ALS cases. [4]

## TREATMENT/ MANAGEMENT

A**s** there is no reversing of ALS the primary goal of treatment is to slow down the disease progression and manage. The secondary consideration is to treat the damage which is already done.

The main aim of management is to improve quality of life, reduce symptoms and improve survival of patient. [13]

## DISEASE MODIFYING TREATMENT

### Riluzole

It is the only drug licensed by FDA (Food and Drug Association)

### Brand name

Rilutek

### Category

Antiglutamatergic agent.

### Mechanism of action

Its exact mechanism of action is unknown. But it reduces the motor neuron damage by decreasing the glutamate release, which reduces the stimulation of

glutamate receptor and regulates the calcium concentration in the neuron intracellularly. This regulation avoids the initiation of apoptosis by mitochondria which are more sensitive to calcium levels. It does not reverse the damage which is already done to motor neuron. It also inhibits effects of excitatory neurotransmitters. [14]

### Adverse effects

- Common
- Stomach upset/diarrhea
- Fever
- Asthenia (lack of energy)
- Abdominal pain
- Liver dysfunction
- Neutropenia
- Decreased lung function
- Arthralgia
- Somnolence
- Circumoral paresthesia
- Rare-
- Hypersensitivity pneumonitis
- Interstitial lung disease (ILD)[14,15]

### Precautions

It should be used with caution in patients with abnormal hepatic function.[14]

### Monitoring

- Complete blood count should be done before initiation of therapy and for every three months.
- Monitoring of serum transaminases for every three month.[14]

### Dosage

50 mg twice daily on empty stomach. [15]

### Pharmacokinetics

- Well absorbed orally
- Protein binding is 96%
- Oral bioavailability is 60%
- Metabolized by liver
- Elimination $t^{1/2}$ ( half-life) is 12 hours
- Excreted in urine 90%, faeces 5%.[15]

### Interactions

- Significant interactions should be monitored closely
- Ciprofloxacin
- Dichlorphenamide
- Fluvoxamine
- Isoniazid
- Pefloxacon
- Teriflunomide.[15]

### Symptomatic treatment

- For limb stiffness- treated with anti-spasticity agent like Baclofen (10mg per day), Tizanidine (1mg TID, maximum 8mg TID).
- For sialorrheoa(excessive salivation)- antisialorrhoea treatment include
  - Salivary gland irradiation
  - Anti-cholinergic like Amitriptyline(25-50mg HS), Trihexyphenidyl(0.5-2 mg as needed)
  - Sympathomimetic like Pseudoephedrine (30-60 mg)
  - Botulinum toxin type B (2500U).
- For thickened secretions- mucolytic can be used to thin thickened secretions such as Guaifenesin. Sometimes removal of secretion require mechanical suction devices.
- For depression and anxiety-
  -for treatment of depression, selective serotonin reuptake inhibitors (SSRI's) like Citalopram (10-40 mg per day).
  -For treatment of anxiety Lorazepam (0.5-1 mg PRN)
- For pain – NSAIDS should be taken.
  -Tramadol, Morphine, Fentanyl patch can be given if symptoms persist.
- For Incontinence-Tolterodine has limited effectiveness.
- For sleeping problems –
  -should first identify whether it is due to ventilatory failure and this can be achieved by overnight polysomnography.
  -Noninvasive ventilatory support is also helpful in this regard.
- Loss of appetite- frequent small meals, food rich in fat and protein should be given.[6]

## VENTILATORY SUPPORT

- The Noninvasive ventilatory support has been recommended which extends and improve the quality of life of patients, when patients experiences ventilatory failure.
- It is most effective than all other treatment for extending life.
- Overnight polysomnography may indicate disruption of closeness of sleep, which is one of

the consequence of ventilatory failure that may be followed by apnea, hypo apnea, nocturnal oxygen desaturation.

- Invasive ventilatory support which requires tracheostomy is recommended in following conditions
- In patients who have respiratory failure and who are neurologically intact.
- For long term invasive ventilatory support to keep patient active.[6]

## DIETARY / NUTRITIONAL MANAGEMENT

As the disease progresses, appetite tends to decline, because ability to swallow is impaired. Therefore dietary supplements are recommended to ensure adequate intake of calories. In patients who have swallowing difficulties and as a result can't maintain adequate calorie intake are recommended for placement of a feeding gastrostomy. [6]

## PREVENTION

Genetic testing and genetic counselling are recommended for individuals with a gene for FALS. As this can decrease the risk of transmitting the gene to next generation. As smoking is only an established risk factor Avoidance of smoking can result in decrease in incidence of ALS. [6]

## TREATMENT APPROACHES

- A wide range of treatment options has been analyzed and examined which includes antioxidants, Anti apoptopic agent and alternative glutamate antagonists. [14]
- Anti-sense therapy is a recent treatment approach which has emerged as very promising strategy to reduce mutant SOD1 protein in patients. [16]
- Stem cell therapy/ stem cell transplants NSI-566 phase II clinical trials are found to be well tolerated. [17]
- Retigabine an anti-epileptic drug which reduces neuronal firing and avoid over excitation is under clinical trials. [18]
- Tirasemtiv which temporarily restore strength for normal activities. [18]
- Tocilizumab – anti-inflammatory drug is under study. [19]

## CONCLUSION

ALS is known to be a complex disease and care of ALS patients are best provided at clinics for managing patients with ALS. From the above evidences, it is rational to attempt the rate of ALS to slow down in people. Currently there is no standard treatment for ALS. The goal is to minimize the rate of ALS progression in the people. The important aspect for alternative therapy for ALS is to change some lifestyle modifications for best results. We hope that the research findings and the undergoing clinical trials will provide hardback treatment which helps to fight this dreadful disease.

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