

# Amyotrophic Lateral Sclerosis - A Narrative Review

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## Abstract

Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's disease is the most commonest type of motor neuron disease represented by progressive weakness of muscles. There occurs degeneration of motor neurons in brain, brainstem and spinal cord. The incidence of ALS is 0.6-3.8 per 100000. The disease has varied clinical presentation which may be limb-onset or bulbar onset. The sensory modalities, sphincter control and ocular involvement is spared. The pathophysiology of the disease is unclear but supported by numerous mechanisms. The role of mitochondrial dysfunction, glutamate excitotoxicity, oxidative stress and crumpling of neurofibrils exists in damaging the motor neurons by apoptosis. The diagnosis of ALS can be established by excluding other disorders mimicking same features and with the help of investigation techniques. The electromyography, nerve conduction studies, neuro imaging and laboratory findings are useful in diagnosing the disease. As there is no cure of this disorder palliative care and rehabilitation forms the mainstay of the management. The management requires multidisciplinary approach involving team members of vast domain including physiotherapists. Physiotherapy has proved to be an effective way of management with the help of compensatory and restorative strategies. The main objective of this paper is to review the literature about ALS and its veiled management.

**Keywords:** Amyotrophic Lateral Sclerosis, Limb onset, El Escorial criteria, Physiotherapy, progressive weakness

## 1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is one of the commonest Motor neuron disease among adults (Susan B. O'Sullivan, Thomas J. Schmitz, 2007). The disease is also known as Lou Gehrig's disease after the name of famous American baseball player Louis Gehrig. The ALS is the most devastating form of MND. In Europe ALS is also known as Charcot's Disease where as in USA this disorder is known as MND. In this, there occurs progressive degeneration of motor neurons in primary cortex, brainstem and spinal cord leading to muscle paralysis. The term amyotrophy means atrophy of muscle fibers because of denervation. It's due to the loss of motor neurons in corresponding anterior horn cells. The term lateral sclerosis refers to deterioration of lateral and anterior corticospinal tracts as these tracts become hard by gliosis. As per reports of the recent studies the incidence of ALS ranges between 0.6 to 3.8 per 100 000 person-years and prevalence is 4.1 and 8.4 per 100 000 per persons. The prevalence and incidence of ALS is increasing. The complete treatment of ALS is not there and most of the patients die 2-5 years after symptom onset, and the only approved drug, riluzole, has a modest effect on survival. A comprehensive and multidisciplinary approach is required to manage ALS clinically (Dal Bello-Haas, 2018). Physiotherapy is the integral component of the rehabilitative approaches. It helps to improve the overall quality of life of the patients (Dal Bello-Haas, 2018).

## 2. Pathophysiology

The pathology of the disease is complex to understand. Previously it was considered that ALS involves degeneration of motor neurons only, but post-mortem reports of many patients suggest that there is a great variation in the expression of this disease in different people. Advanced imaging techniques depicted the evidence of involvement of non motor areas such as extrapyramidal tracts as well. Apart from this other non motor areas involved are basal ganglia, cerebellum, autonomic nervous system and oculomotor and sensory system. (ALS PT ref) The pathogenesis of the disease involve the mechanisms including transformed signaling pathways, such as dysfunction of mitochondria, glutamate excite toxicity, oxidative stress and

neuro inflammation. Genetic mutation also play role in expression of ALS. Recent studies have found 20 gene types including SOD1 which are responsible for ALS disorder. There are different hypothesis that are believed to cause the disorder. The first and foremost hypothesis is mitochondrial dysfunction. Apart from being the power houses of the cells mitochondria releases ROS (reactive oxygen species) which have a role to play in apoptosis. Therefore, structural and metabolic alteration in mitochondria may be related to some features of ALS. The second belief is glutamate excitotoxicity. The genetic mutation results in increased synaptic glutamate concentration and an over-stimulation of glutamate postsynaptic receptors, which determine the excitotoxic degeneration of neurons in the motor synaptic clefts. The third hypothesis is oxidative stress by free radicals. When the ROS over accumulates and does not gets removed it leads to irreversible damage to the structure of the cells and its proteins such as DNA and RNA. In addition to this, the clumping of neurofilaments in the cell bodies and axons are also responsible for the neuronal damage. Finally the reactive astrocytosis is also considered to be one of the mechanisms leading to neuronal cell death. In a nutshell, the exact pathogenesis is difficult to explain but there are multiple mechanisms which contribute in varied expression of disease in different patients (Bonafede & Mariotti, 2017)(Morgan & Orrell, 2016).

### 3. Clinical presentation

The disease usually begins after the fourth decade. The mean or median age of onset is 51 to 66 years. The disease begins with progressive muscle weakness due to degeneration of motor neurons in upper as well as lower motor neurons. The LMN degeneration causes symptoms such as fasciculation, cramps, muscle atrophy and marked weakness. On the contrary the UMN degeneration causes spasticity, hyper-reflexia, positive Babinski and Hoffmann signs along with modest weakness. Depending upon the initiation of symptoms the clinical presentation may be discussed as limb-onset or bulbar onset. The limb onset is presented in two third of the patients (Allan H.Ropper, Robert H. Brown, 2005). The peculiar feature of this disease is asymmetrical and focal weakness beginning in the arms.(Fox, Ebersbach, Ramig, & Sapir, 2012) The lower limb weakness is followed by upper limbs. The weakness in lower limbs and foot drop is the reason for difficulty in walking making them more prone for falls. In Bulbar Onset presentation is expressed by women more than men and have poor prognosis. Dysarthria is the pioneer feature which is seen followed by dysphagia and over drooling of saliva. The writhing movements of atrophied tongue is considered as a specific feature of Bulbar-Onset ALS (Coupé & Gordon, 2013). No matter what the disease usually progresses from one form to the other and eventually involves respiratory muscles leading to death of the patients. The sphincter control and eye movements are spared along with preservation of sensory modalities. Apart from these frontotemporal dementia is also seen in which cognitive deterioration in language, memory, judgement and personality are seen. As the condition is highly morbid patients usually exhibit depression and emotional lability.

### 4. Diagnosis

The diagnosis of ALS is established on the basis of clinical evaluation and laboratory investigations. The El Escorial criteria provides a standard to establish the diagnosis (Coupé & Gordon, 2013).The criteria is described in Table 1.

Table 1 El Escorial criteria for ALS diagnosis:

Clinically possible ALS	UMN and LMN signs in one region, or UMN signs in at least two regions, or UMN and LMN signs in two regions with no UMN signs rostral to LMN signs
Laboratory-supported probable ALS	UMN signs in one or more regions and LMN signs defined by EMG in at least two regions
Clinically probable ALS	UMN and LMN signs in two regions with some UMN signs rostral to the LMN signs
Clinically definite ALS	UMN and LMN signs in three regions

The clinical evaluation is done by using sensory motor assessment techniques. Apart from clinical examination electrophysiological diagnosis should be performed which helps to exclude the other diseases mimicking similar features. Sensory motor nerve conduction studies helps to exclude the other reasons of peripheral nerve and neuromuscular junctional disorders which may confound the condition. As per El diagnostic criteria also the muscle degeneration must be supported by EMG findings. The abnormal findings constitute fibrillation potential and positive sharp waves in acute case whereas increased amplitude along with duration of motor unit action potential and unstable motor unit potentials in chronic cases. The treatable structural lesions must be excluded using neuroimaging. Apart from this hyperintensity of corticospinal tracts are confirmed using T2 MRI scan. The muscle biopsy is not advisable in routine examination but it also helps to exclude the other diseases presenting with same features. Additionally, for more accuracy the laboratory findings of muscle enzymes such as Serum creatinine, hypochloremia and elevated CSF proteins may be promising (Wijesekera & Leigh, 2009).

### 5. Differential diagnosis

There are numerous other disorders which mimic the features of ALS. Therefore, the differential diagnosis may be established on the basis of anatomy, clinical presentation and symptoms. Some of the diseases are listed below (Majid Ghasemi, 2016):

- 1) Adult polyglucosan body disease (APBD)
- 2) Adrenomyeloneuropathy
- 3) Multiple Sclerosis
- 4) Syringomyelia
- 5) Kennedy's disease
- 6) Lymphoma
- 7) Paraneoplastic encephalomyelitis
- 8) Peripheral neuropathies
- 9) Neuromuscular junction disorder
- 10) Oculopharyngeal muscular dystrophy
- 11) Hyperthyroidism

All the disorders are excluded on the basis of clinical findings, disease course and investigations as in ALS asymmetric weakness is presented by most of the cases.

## 6. Management

The diverse and complex nature of the disease requires comprehensive and multidisciplinary approach of management(Martin et al., 2017). The disease has no cure till date which makes the management even more challenging. The multidisciplinary team consists of Neurologist, physical therapist, occupational therapist, social worker, Counsellor, Respiratory therapist, Pharmacists etc.(Susan B. O'Sullivan,Thomas J. Schmitz, 2007) The Disease modifying agents such as Riluzole, which is a glutamate inhibitor have proved to be effective but then also it cannot completely cure the disease. The management paradigm hence depends upon palliative care and rehabilitation. The medical management is symptomatic and cater to individual impairments depending upon different patients. Anti-cramping medications, anti spasticity agents, drying agents for sialorrhea, and antidepressants are commonly used (Lau, Brennan, & Gardiner, 2018). The rehabilitation of ALS using Physiotherapy may be designed on the basis of staging the disease into early, middle and late stages based upon impairments, activity limitations and participation restrictions. The focus should be on framing realistic goals with address individual patient's needs. The physiotherapy rehabilitation may be provided as follows:

### Early Stage:

Mild to moderate weakness can be seen in specific muscle groups at this stage. The patients find it difficult to perform daily activities and by the end of this stage they progress to difficulty in mobility. The physiotherapy rehabilitation should be framed using compensatory and restorative approaches. Active Range of motion (ROM) exercises, active assisted exercise, stretching, strengthening and endurance exercises are used as restorative techniques where as energy conservation, assistive devices and ergonomics are used as compensatory strategies.

### Middle Stage:

In this stage the patients presents with progressive reduction in mobility where wheel chair may be required to commute for long distances. The muscle weakness also becomes severe in some muscle groups which further reduces the efficiency of patients to perform the activities of daily living. The framework of therapy here comprises of more dependence on supportive devices such as slings and orthoses, workplace modification and education of care givers as compensatory strategies. The preventive approach is introduced in this stage by incorporating exercises for remaining groups to prevent further damage.

### Late Stage:

This is the advance stage of disease in which the patients are restricted to bed with complete dependence of ADL. Severe weakness of muscles along with dysphagia and dysarthria further complicates the condition. This stage also presents with respiratory compromises. The mainstay of this stage is compensatory and preventive. But chest PT, positioning may be used as restorative techniques for respiratory problems. The compensatory strategies which may be used are care giver education, mechanical lifting of the patients and skin care due to bed ridden condition(Susan B. O'Sullivan,Thomas J. Schmitz, 2007).

## 7. Conclusion

There are various conditions which mimic ALS. Due to lack of better understanding of this condition, it is often unrecognized or misdiagnosed. Presently, the need to write this paper was to expand knowledge and increase publicity about the condition and its underlying management. Apart from misdiagnosis, the late interventions reduces the life span of the patients which undoubtedly lead to a depressing situation. Lack of expertise in diagnosing and managing these cases also lead to suffering of numerous patients. Apart from medications, there exists evidence which supports non pharmacological interventions such as rehabilitation. The clinical practise guidelines have been provided to address the patient's impairments. Tailoring a holistic rehabilitative protocol including exercises, adaptive and assistive devices, patient and family education, psychological counselling and using compensatory strategies may help to enhance patient's quality of life.

## Conflict of Interest

The authors have no actual or potential conflicts of Interest.

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