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Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is progressive neurodegenerative disease affecting motor neurons. Although the cause of ALS is not completely understood, recent research suggests that multiple complex factors contribute to the death of motor neurons. Specific risk factors for ALS have not been conclusively identified, but ongoing research is exploring the possible role of genetics and/or environmental factors. This progression degeneration leads to muscular atrophy and cessation of control of voluntary movements. Currently, approximately 30,000 Americans have been inflicted with the disease. Most patients with ALS have a median survival of about three years after onset following death due to respiratory failure. There has been an overlap in the underlying molecular mechanisms between ALS and frontotemporal dementia or FTD having clinically common manifestations like behavioral changes, impairment of executive functioning and language impairment. There are broadly two types of ALS: (1) familial ALS or fALS, and (2) sporadic ALS or sALS. Both ALS incidence and prevalence in males were found to be higher than that of females. Mean age at onset of symptoms is 58–63 years for sporadic ALS (sALS) and 40–60 years for familial ALS (fALS), respectively. ALS is caused by a combination of genetic factors, environmental factors and aging-related dysfunction. Only 5 to 10 percent of all ALS cases are familial. About 25-40% of all familial cases as well as a small percentage of sporadic cases are caused by a mutation in a gene *C9ORF72*. Another 12-20% of familial cases are caused by mutations in the gene that provides instructions for the production of the enzyme copper-zinc superoxide dismutase 1 (*SOD1*). Considering other genetic risk factors for ALS, patients with genotype *UNC13A* maybe susceptible to getting the disease. Environmental risk factors behind ALS include smoking, body mass index, physical exercise, occupational and environmental exposures to metals, pesticides, β-methylamino-L-alanine, head injury and certain viral infections. Diagnosis is primarily based on the examination of medical history, physical examination, electrodiagnostic testing (with needle EMG) and neuroimaging. Patients with a positive family history of ALS are advised to get genetic testing done for the five most prevalent genes found to be mutated in ALS (C9orf72, SOD1, TDP43, FUS, TBK1). As a neurodegenerative disease ALS has no cure, therefore management of patients with symptomatic

treatment along with proper care including respiratory, nutritional and exercise management is recommended.

Introduction

Amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease, is a heterogeneous neurodegenerative disease affecting primarily both upper motor neurons, lower motor neurons and the central nervous system (CNS) leading to motor and extra-motor symptoms. ALS is characterized by a gradual degeneration of motor neurons, leading to neuronal death. Motor neurons extend from the brain to the spinal cord and to the muscles throughout our body. The motor neurons are responsible for communication between the brain and the voluntary muscles. Messages from the brain are transmitted by the upper motor neurons (neurons that project from the cortex to the brainstem and the spinal cord) and lower motor neurons (neurons that project from the brainstem or spinal cord to muscle) to the spinal cord and motor nuclei of the brain and finally to a particular muscle or group of muscles. In ALS, this signal transmission from the brain to the muscles is disrupted due to degeneration of both the upper and the lower motor neurons. Due to the subsequent loss of function, the muscles gradually become weak, twitch (called fasciculations, Figure 1 below), and muscular atrophy occurs. The brain eventually loses its ability to initiate and control voluntary movements. The weakness most commonly starts in the distal limb muscles rather than in the proximal muscles. When symptoms begin in the arms or legs, it is referred to as "limb onset" ALS. Other individuals first notice speech or swallowing problems, termed it as "bulbar onset" ALS. A bulbar onset of the disease is reported in 25%–30% of cases, which includes dysarthria, dysphagia, dysphonia, or more rarely masseter weakness. The age at onset, the site of onset and the disease progression rate of ALS varies widely. In most patients, ALS advances relentlessly, with a median survival of about 3 years after onset, and in most cases death is due to respiratory
failure. [1]

Extensive population analysis based on phenotypic data, highlights the fact that almost 50% of patients with ALS present extra-motor manifestations such as cognitive and/or behavioral impairment. About 13% patients develop concomitant behavioral variant frontotemporal dementia (FTD) while 35%–40% patients show mild behavioral and/or cognitive changes [2, 3].

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FTD causes degeneration of the frontal and anterior temporal lobes and is clinically manifested by behavioral changes, impairment of executive functioning and language impairment [4]. Overlap in the underlying molecular mechanisms has been observed in both these neurodegenerative disorders, namely ALS and FTD [5].

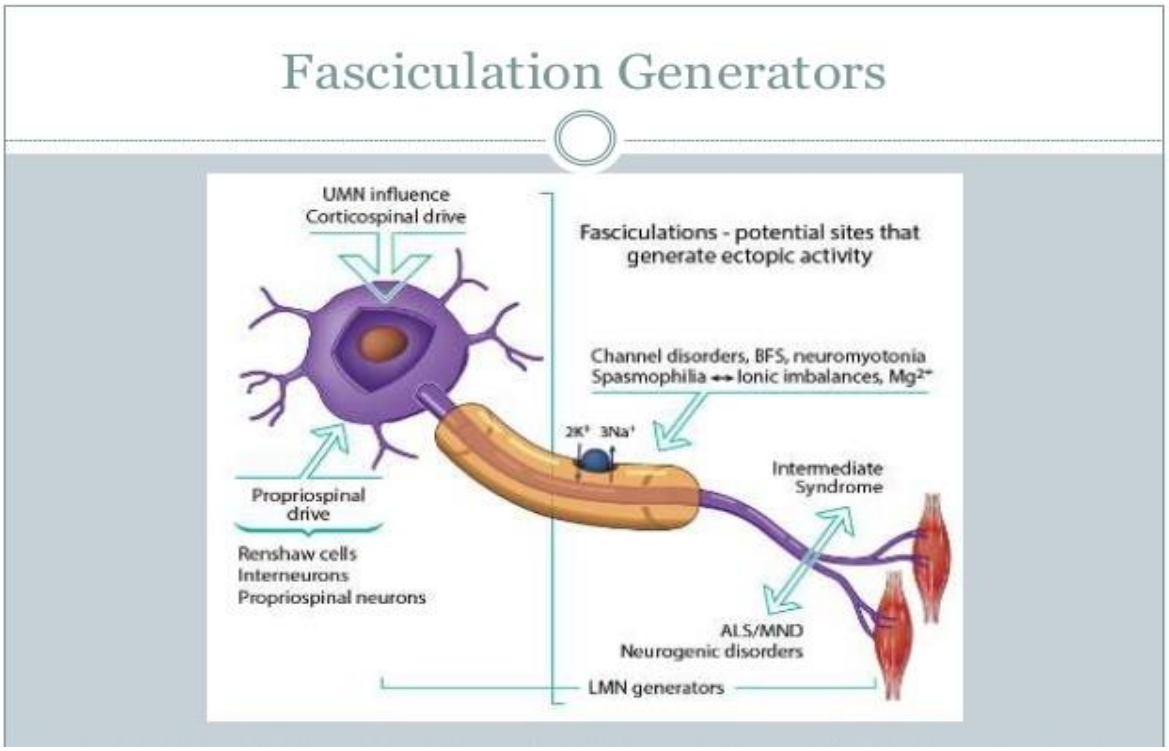

Figure 1: **Fasciculation Generators** (Reference no. [1])

Epidemiological Data

The global ALS prevalence and incidence are approximately 4.42 per 100,000 people and 1.59 per 100,000 person-years, respectively. Both ALS incidence and prevalence of males (incidence: 1.91, 95% CI 1.65–2.19; prevalence: 5.96, 95% CI 5.14–6.85) were found to be higher than the corresponding values of females (incidence: 1.36, 95% CI 1.14–1.59; prevalence: 3.90, 95% CI 3.30–4.56) [6]. Based on U.S. population studies, annual incidence is about 2 per 100,000 people and prevalence is 5 per 100,000 in the United States. These figures suggest that approximately 30,000 Americans currently have the disease. Every 90 minutes, someone is diagnosed with the disease and someone passes away from it. In Europe, the incidence of ALS is higher, ranging from 2.1 to 3.8 per 100,000 people per year and a prevalence of 10–12 per 100,000 in Europe,

but there are significant geographical differences [1, 7]. Worldwide the incidence amounts to 4–8 per 100,000 people per year in the age group with the highest risk of developing ALS (45–75 years). Mean age at onset of symptoms is variable: 58–63 years for sporadic ALS (sALS) and 40–60 years for familial ALS (fALS) [8]. An estimation of the cumulative lifetime risk for developing ALS is 1:350 in men and 1:400 in women [9,10]. Men have a higher risk of developing sporadic ALS compared to women; the global sex ratio being 1.2–1.5 [11].

Types of ALS

Sporadic ALS (sALS)

Most of the ALS cases (90 percent or more) are considered to be sporadic which means that the disease seems to occur at random with no family history of the disease. However, family members of people with sporadic ALS (sALS) are at an increased risk for the disease.

Familial ALS (fALS)

Only 5 to 10 percent of all ALS cases are familial, which means that the disease is inherited from parents. The familial form of ALS usually only requires one parent to carry the gene responsible for the disease. Mutations in more than a dozen genes have been found to cause familial ALS. About 25 to 40 percent of all familial cases (and a small percentage of sporadic cases) are caused by a mutation in a gene known as "chromosome 9 open reading frame 72," or *C9ORF72*. Interestingly, the same mutation can be associated with atrophy of frontal-temporal lobes of the brain causing frontal-temporal lobe dementia. Some individuals carrying this mutation may show signs of both ALS and FTD. Another 12 to 20 percent of familial cases are caused by mutations in the gene that provides instructions for the production of the enzyme copper-zinc superoxide dismutase 1 (*SOD1*).

Etiology

ALS is caused by a combination of genetic factors, environmental factors and aging-related dysfunction. At the genetic level, to date over 20 genes have been linked with the disease, and research is still going on. The overall heritability of ALS is high; in patients with sALS the heritability is estimated to be 30%–60% [12, 13]. The risk of developing ALS doubles in first degree relatives of ALS patients [13].

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Autosomal dominant causes of ALS

The first ALS-related gene *SOD1* was discovered in 1993. SOD1 mutation is responsible for almost 20% of fALS and 1%–2% of sALS [14]. Mutations in *SOD1* gene causes aggregation of the protein SOD1 which disturbs multiple important cellular functions thus leading to pathophysiologies of ALS. Subsequently mutations in *TARDBP* and *FUS* genes were discovered to be responsible for 3%–5% of fALS and for <1% of sALS [15–18]. Furthermore, mutations in *C9ORF72* gene were discovered to be responsible for 30%–50% of fALS and for 7%–10% of sALS [19, 20]. The fifth most common cause of autosomal dominant ALS is mutation in *TBK1* gene which is responsible for about 1% of ALS patients [21, 22]. Usually ALS patients are not found to carry mutations in more than one of these genes, suggesting that ALS can be oligogenic in origin [23, 24].

Risk factors

As far as the genetic risk factors for ALS are considered, the genotype *UNC13A* is at risk [25], and the presence of a mutation in the *ATXN2* gene increase the risk of developing ALS [26, 27]. Statistics show that age and male sex increase the risk for ALS. Furthermore, smoking, body mass index, physical exercise, occupational and environmental exposures to metals, pesticides, β-methylamino-L-alanine, head injury and certain viral infections have been pointed out as environmental risk factors for ALS [28–30]. However, the specific relationship between these factors and ALS has yet to be established.

Pathogenesis

ALS is characterized by loss of the neuromuscular connection, axonal retraction and subsequent cell death of upper and lower motor neurons, accompanied by astrogliosis and microgliosis In addition, ubiquitin-positive inclusions are detected in the surviving neurons. In order to understand the disease progression and for the development of new therapeutic approaches, it is imperative to first delineate the underlying molecular mechanisms by which motor neurons degenerate in ALS. SOD1 mutations have been reported to be associated with ALS for more than two decades now. However, the mode of action of mutant SOD1 and the subsequent mechanism of neurodegeneration or neurotoxicity is yet to be fully determined. Scientists currently believe that the combination of several mechanisms, instead of a single mechanism, contributes to

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neurodegeneration in ALS, thus indicating the possibility of multifactorial pathogenesis (Figure 2).

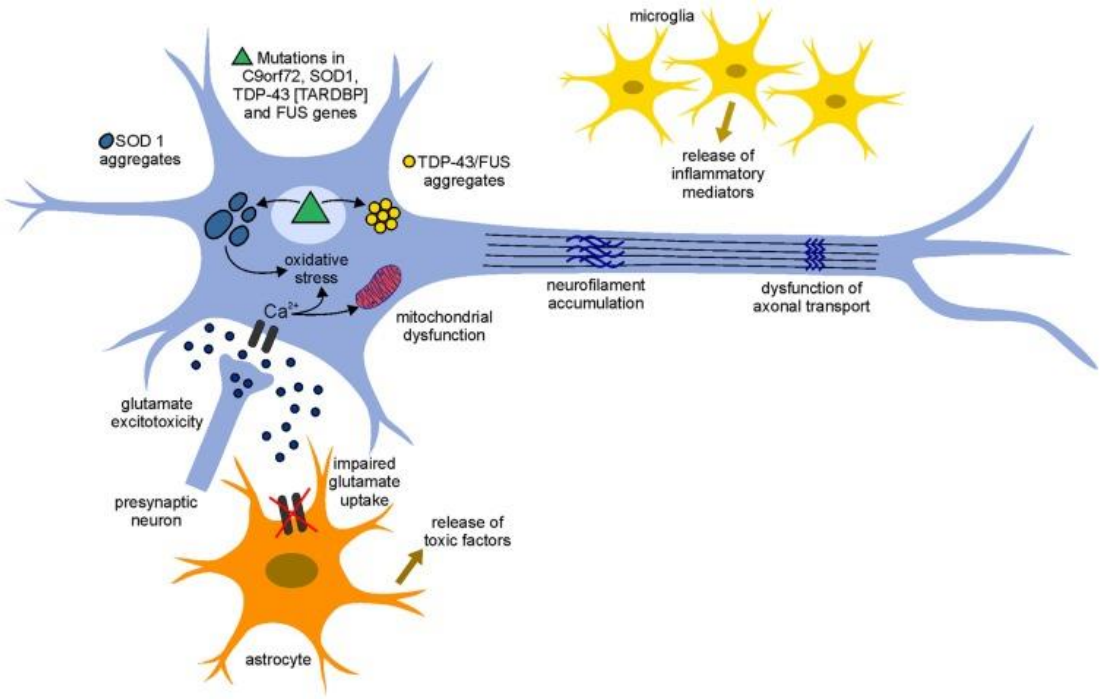

Figure 2. **Pathogenesis involved in amyotrophic lateral sclerosis (ALS)** (Reference no. [69])**.**

Mitochondrial Dysfunction

Mitochondrial damage is one of the hallmarks of ALS. This impairment arises from the presence of reactive oxygen species (ROS) and other metabolic and structural changes in the cell leading to neuronal damage. Structural changes in mitochondria are observed in spinal motor neurons and skeletal muscle of both sALS and fALS patients as well as in the murine model of the disease [31-33]. In ALS transgenic mice as well as patients, deposition of misfolded mutated SOD1 protein may alter the physiological function of mitochondria [34]. Additionally, mutated SOD1 is responsible for decreased activity of respiratory chain complexes I and IV which can be associated with defective energy metabolism. In ALS patients it has been reported that there is a loss of Ca2+ binding proteins in the motor neurons as a result of the presence of mutated SOD1, which leads to reduced calcium uptake from the cytoplasm subsequently increasing the

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sensitivity to excitotoxicity [35, 36]. Mitochondria are also an integral part of synaptic terminals which require high amount of ATP and calcium homeostasis. Defects in mitochondrial axonal transport to these areas may lead to metabolic alterations in neurons and cell death [37].

Glutamate Excitotoxicity

Glutamate is the main excitatory neurotransmitter of the central nervous system (CNS). It is synthesized in the presynaptic terminal and subsequently activates specific postsynaptic receptors leading to neurotransmission via voltage gated calcium channels. Unused glutamate is removed from the synaptic cleft; post its release from the presynaptic neuron, by excitatory amino acid transporters (EAATs) which are primarily glial and neuronal cell transporter proteins. Reports suggested that the excess concentration of glutamate in the synaptic cleft leads to excitotoxicity because excessive or extensive activation of glutamate receptors, which can cause neurodegeneration of the involved neurons [38]. Therefore, it is necessary to remove the glutamate rapidly in order to prevent neuronal toxicity. Specifically, EAAT2, isoform 2 of the astroglial glutamate transporter, is responsible for maintaining the glutamate below excitotoxic levels in the nervous system [39]. Glutamate excitotoxicity was one of the first proposed mechanisms involved in pathogenesis of ALS [40]. Literature suggested that the motor cortex and spinal cord of ALS patients were reported to display reduced EAAT2 levels, probably due to the presence of aberrant EAAT2 mRNA or due to EAAT2 transporter cleavage. This results in an increase of synaptic glutamate concentration and over-stimulation of glutamate postsynaptic receptors, which leads to excitotoxic neuronal degeneration [41]. Irregularities in glutamate and its associated regulatory proteins in the neurotransmitter cascade contribute to glutamate excitotoxicity in motor neuron degeneration and disease progression in ALS.

Oxidative Stress

Oxygen metabolism generates free radicals or ROS. The condition where the amount of ROS generated is higher than the capacity of cells to remove the ROS is termed as oxidative stress. The accumulation of ROS causes irreversible damage to the cell as well as its macromolecules, including proteins, DNA and RNA. SOD1 is the primary enzyme that prevents oxidative damage and reduces superoxide leakage from mitochondria. Thus mutations in SOD1 can lead to cytotoxicity. Early studies suggested that not only a decrease/loss in the enzymatic function of SOD1, but also a dominant toxic gain of function of the enzyme may be involved in ALS pathogenesis [42]. One hypothesis claims that mutant SOD1 could revert back to its normal

antioxidant activity thus giving rise to toxic superoxide. Mutated SOD1 could take electrons from other cellular antioxidants and donate them to molecular oxygen thus producing superoxide and making SOD1 the source of oxidative stress [43, 44]. Increased levels of free radicals and consequent oxidative damage were found in cerebrospinal fluid (CSF), serum and urine samples of ALS patients [45]. This may be caused by an altered geometry in the active site of the mutated SOD1, which allows entry of reducing substrates. Moreover, another cause of oxidative stress in ALS may be a defective oxidative phosphorylation, as reported by studies on CSF in transgenic mice and in patients, in which ROS produced from defective oxidative phosphorylation, such as 3-nitrotyrosine, were observed to be present in high concentration [46, 47]. The increase of ROS correlates with mitochondrial dysfunction and provides an example of how different mechanisms of pathogenesis of ALS may be interconnected.

Protein Aggregates

Protein aggregates are formed by accumulation of misfolded proteins, which oligomerize and aggregate, forming a toxic environment around the neurons. Mutated SOD1 protein-rich inclusions have been found in both sALS and fALS tissues as well as in mutant SOD1 transgenic mice [48]. The aberrant accumulation of mutated proteins leads to lack of their degradation, which results in formation of aggregates consisting of mutated SOD1 and other mutated nuclear proteins like TDP43 or FUS. TDP43 aberrant protein inclusions are found in 80% of ALS cases, where the protein was found in cytoplasm leading to abrupt accumulation [49]. Similarly, FUS is also another nuclear protein, which upon mutation leads to cytoplasmic accumulation [50]. Taken together, protein inclusions and aberrant accumulation in ALS is a major cause of motor neuron degeneration and death.

Accumulation of Neurofilaments

Accumulation of neurofilaments (NFs) in the cell bodies and axons is a typical pathological feature of ALS. NFs are the intermediate filaments of nerve cells and an important part of the nerve cell cytoskeleton [51]. The process that leads to formation of NF aggregates in ALS is still unclear. Mutations in NF genes occur in both fALS and sALS and may be correlated to abnormal phosphorylation of NFs which affects the axonal transport of NFs, leading to their accumulation in the cell bodies and proximal axon. This accumulation may lead to defects in axonal transport of other cellular components essential for cell survival, like mitochondria [52]. Another cause for the aggregation of NFs may be their altered stoichiometry which plays a pivotal role in the

distribution and aggregation of NFs. The abnormal organization of NF is an important part of the pathogenesis of ALS, however the exact relationship between their accumulation and motor neuron degeneration still remains unclear.

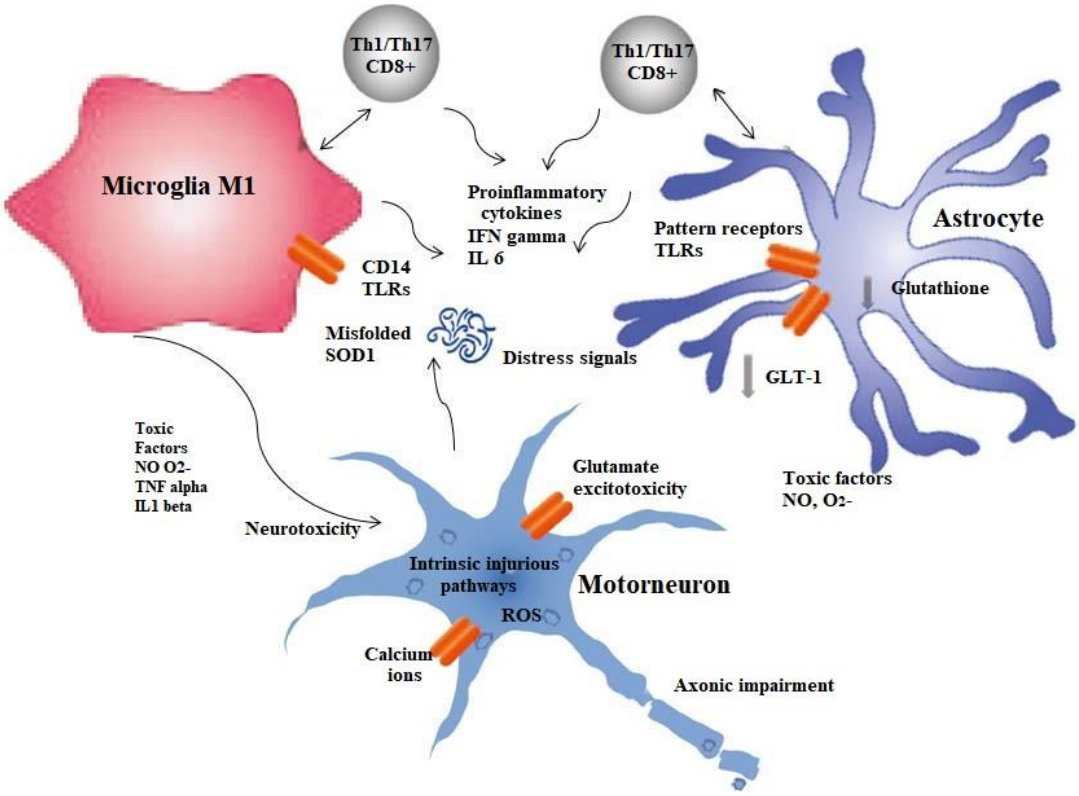

Figure 3. **Cytotoxic phase of Neuroinflammations in amyotrophic lateral sclerosis(ALS**) (Modified from Reference [70]).

Neuroinflammation

Neuroinflammatory response, including activated microglia, astrogliosis and infiltrating immune cells in the sites of neuronal injury, is one of the primary features of ALS. Motor neurons which are not mutated but are surrounded by glial cells with SOD1 mutated gene develop the

pathological phenotype. Moreover, the replacement of mutated glial cells with wild-type glia was reported to delay disease progression and prolong survival in ALS mice. Thus, damaged glia and neurons are together involved in the process of neurodegeneration and to disease progression [53]. In ALS the interaction between motoneurons and microglia, which are the resident macrophages in the CNS, initially protects neurons. As the damage worsens, misfolded proteins, like mutated SOD1, and other toxic molecules are released from the motor neurons and astrocytes that stimulate the activation of microglial cells, which switch from the neuroprotective to a neurotoxic phenotype [54]. Thus, activated microglia increase during disease progression as a result of their interaction with the cellular microenvironment, leading to a cytotoxic neuroinflammatory effect on the neurons (Figure 3) .

Clinical presentation

The characteristic features of ALS include weakness, atrophy, twitches, cramps and stiffness of muscles leading to slowness of movements. This onset of muscle weakness usually occurs at one particular site in the body and then spreads to adjacent regions. There are mainly two types of clinical presentations of the disease: (1) spinal ALS which occurs in roughly in two-thirds of patients and is presented with unilateral distal muscle weakness and atrophy in upper or lower limb muscles; and (2) bulbar ALS which occurs in bulbar muscles and is reported in about one-third of the patients. The onset of the disease is most common in the upper limb of the dominant hand where the thenar muscles are more affected than hypothenar muscles, a characteristic which is referred to as the split-hand syndrome [55]. Additionally, the first interosseous muscle is involved at the early stage and the finger extensors observed to be more affected than finger flexors [56]. As the disease progresses to the lower limb, the anterior tibial muscle is affected earlier than the gastrocnemius muscle and the hamstrings are affected before the quadriceps muscles [57]. The most common clinical presentation of bulbar ALS is dysarthria or dysphagia, while dysphonia in not so commonly observed, along with reduced mouth closure or chewing problems. Axial muscle weakness alongside head drop and difficulty in maintaining posture are common in later stages of the disease. About one-third of patients demonstrate a case of pseudobulbar affect, which means that there can be bouts of uncontrolled laughing or crying. In some cases, muscle twitches and cramps or mild weight loss may precede muscle weakness.

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A neurological examination of patients with classic ALS shows a combination of signs of upper motor neuron (UMN) and lower motor neuron (LMN) involvement. The signs of LMN involvement are muscle weakness, atrophy, twitches (fasciculation) and reduced muscle tone. Whereas the signs of UMN involvement include hyperreflexia (or retained reflexes in atrophic muscles), increased muscle tone (especially in upper limb flexors and lower limb extensors) and slowness of movements (especially in tongue movement). The majority of patients are reported to show a classic ALS phenotype with spinal or bulbar onset. Recent research has shown that there are several etiologies of ALS, hence it is a clinically heterogeneous disease with recognizable motor and extra-motor manifestations (Figure 4). Even the motor manifestations of the disease vary considerably, accompanied by variable degrees of frontotemporal involvement, which leads to different phenotypic representations of the disease and have different disease trajectories. To date no widely accepted clinical criteria for the different ALS phenotypes exist.

Phenotypes of ALS

Several distinct phenotypes of ALS exist. The phenotypes are mainly classified based on the involvement of upper and lower motor neurons.

Subtypes of ALS based on relative UMN and LMN Involvement

Classic ALS is observed with signs of combined UMN and LMN loss in one or more regions of the patient's body. Clinical examination reveals primary lateral sclerosis (PLS), characterized by progressive spasticity and slowing movements with isolated signs of UMN. In this case there is no muscle atrophy or visible fasciculations, and no signs of denervation observed on electromyography (EMG) four years from symptom onset. The symptoms usually begin symmetrically in the lower limbs but can also begin in the bulbar region. Nearly 3%–5% of all motor neuron diseases are PLS and can evolve into ALS, typically within 3-4 years after onset of the disease. UMN predominant ALS patients also exhibit certain features involving LMN but nowhere as significant as the UMN features. The lifespan of these patients is shorter in comparison to PLS, but they show a slower rate of disease progression compared to classic ALS.

Similarly, LMN predominant ALS patients show minimal signs of UMN involvement and have different rates of progression. Furthermore, progressive muscular atrophy can be identified by

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specific progressive LMN signs but no clinical manifestation of UMN dysfunction at the onset; however, almost 30% of these patients tend to develop UMN signs during follow up.

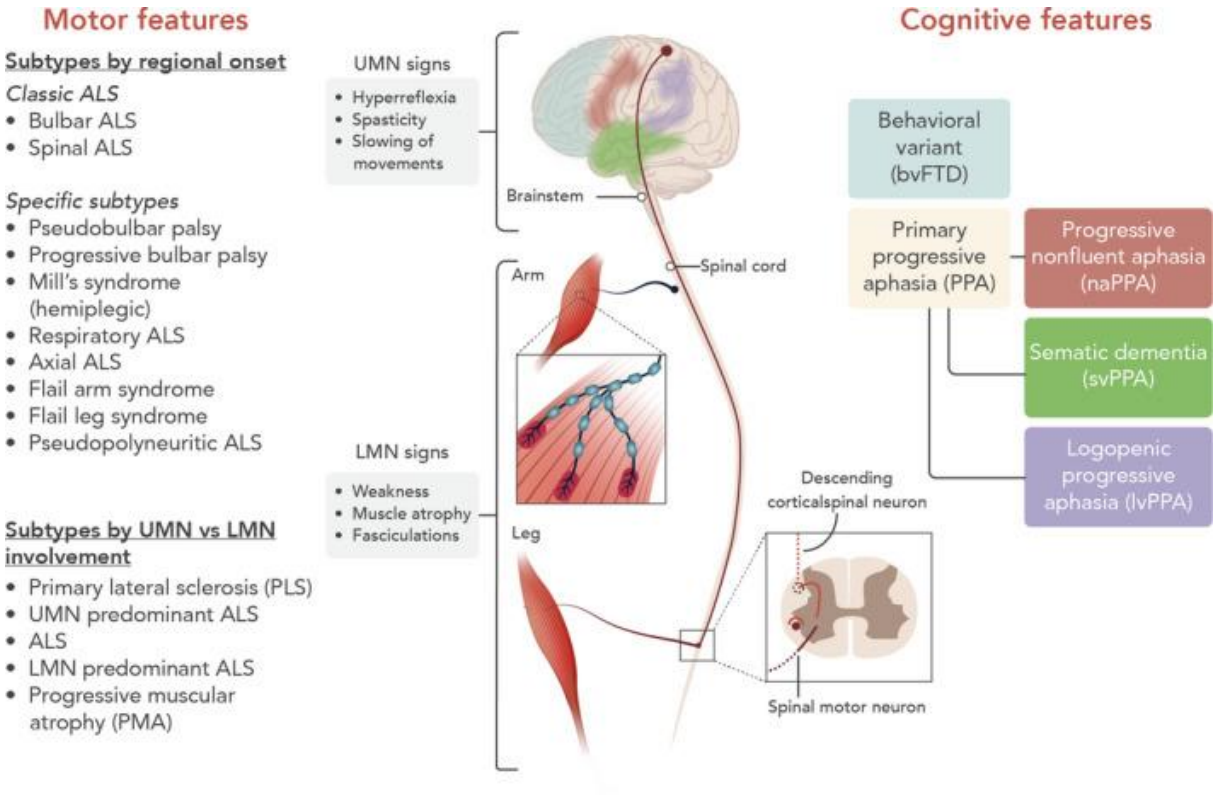

Figure 4. **Clinical presentations of ALS.** (Reference no. [1])

Subtypes of motor neuron disease based on regional distribution of involvement

Bulbar ALS is characterized by a rapid disease progression and a median survival of 2 years from onset. Clinical manifestation of bulbar UMN dysfunction is spastic dysarthria, which is marked by slow, labored and distorted speech. On the other hand, patients with bulbar LMN dysfunction show tongue wasting and fasciculation, accompanied by flaccid dysarthria and dysphagia. Pseudobulbar palsy patients demonstrate absence of facial expressions, spastic dysarthria, difficulty in chewing, dysphagia and tongue protrusion due to spasticity, but no tongue fasciculation or wasting is observed [58]. Unlike progressive bulbar palsy, where the LMNs are affected, in the case of pseudobulbar palsy, UMNs are involved and hence the jaw jerk is exaggerated. Mill's syndrome (hemiplegic variant) presents a hemiplegic or asymmetrical

pattern of involvement in patients. For this disease subtype, the symptoms gradually progress, and it is more ascending than descending. Pyramidal signs are typically dominant along with hemiplegia. Diaphragm weakness (e.g. dyspnea at exertion, dyspnea at rest or orthopnea) may be observed in only about 3% of ALS patients as the initial problem (respiratory ALS), and these patients have a poor prognosis. In axial variant ALS, the onset of the disease is in the paravertebral muscles, with stooped posture as a presenting symptom. Flail arm ALS (brachial amyotrophic diplegia, man in the barrel syndrome or Vulpian–Bernhardt syndrome) is characterized by an LMN pattern of weakness in the upper limbs, a mostly symmetrical pattern of weakness that usually begins in proximal muscles and progresses on to distal muscles. Bulbar symptoms develop in almost 77% of these cases and it is mostly predominant in males than in females (male to female ratio 3:1) [59]. Flail leg ALS is characterized by progressive, asymmetrical, predominantly LMN pattern of weakness with distal-onset of the weakness and wasting in the lower limbs. No significant weakness or wasting is observed in the upper limbs and bulbar region within 12 months after onset and the disease progression is slightly than classic ALS. Clinical manifestations of pseudopolyneuritic ALS are distal weakness of the lower limbs and absence of Achilles tendon reflex, along with notable peripheral neuropathy.

Subtypes of ALS based on additional frontotemporal involvement

FTD is the most common cause of dementia after Alzheimer's disease in patients under age 65. In case of 50% of ALS patients, the degenerative process can extend to the frontal and anterior temporal lobes, resulting in variable degree of executive dysfunction, language impairments or behavioral changes (Figure 2). About 50% of patients show normal cognition but about 10%–15% are diagnosed with ALS-FTD, when the criteria for behavioral variant FTD or criteria for primary progressive aphasia are fulfilled [60].

Diagnosis

ALS may be diagnosed based on the medical history, physical examination, electrodiagnostic testing (with needle EMG) and neuroimaging. EMG is one of the useful diagnostic tools to confirm the involvement of lower motor neurons in clinically affected and non-affected muscles (with fibrillation potentials, sharp [61]).

Biomarkers play a crucial role in diagnostic, prognostic as well as predictive research studies. Although it has not yet been established as a standard clinical practice, several biomarkers such as cerebrospinal fluid neurofilament levels (especially phosphorylated neurofilament heavy subunit) are useful in supporting the diagnosis, particularly in patients with recent onset of muscle weakness, without clear signs of UMN involvement, or with concomitant neuropathy/plexopathy/cervical myelopathy [62, 63]. In specific cases brain and spinal cord magnetic resonance imaging are performed to exclude structural lesions affecting the motor system. Furthermore, ^{18}Ffluorodeoxyglucose (^{18}FFDG) positron emission tomography maybe used to reveal a typical pattern of hypometabolism in Rolandic brain regions and frontotemporal involvement [64, 65].

Patients with a positive family history of ALS are advised to get genetic testing done for the five most prevalent genes found to be mutated in ALS (C9orf72, SOD1, TDP43, FUS, TBK1). But there is as yet no consensus on genetic testing for patients with sALS. However, doctors advise genetic testing only when genetic counselling can be provided in case a pathogenic gene mutation is identified.

Clinical Management for ALS

The management of ALS requires multidisciplinary care. Since no cure has yet been established, providing multidisciplinary care, including respiratory management, has been found to improve quality of life and survival in ALS patients.

Pharmacological Treatment

Considering ALS as a chronic neurodegenerative disease, disease modifiable measures and aids with proper equipment and patient care for symptomatic relief is the only treatment. The current FDA approved drugs are Riluzole and Edaravone. Although these medications cannot reverse or stop progression of ALS, but they can give symptomatic benefits [66]. A report suggested from randomized clinical trial data on Riluzole showed 35% improved twelve months' survival rates and was well tolerated. However, it is very expensive. Edaravone, utilized as a free radical scavenger, exhibited reduced motor decline and is perfectly tolerable with minimal side effects. However, the drug requires an intravenous mode of administration. A survey revealed

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Edaravone was given to 59% of the ALS patients through an implanted port; to another 21% of ALS patients through a peripherally inserted central catheter (PICC); 18% of ALS patients were administered Edaravone through a peripheral line, while the remaining 2% of ALS patients were administered the drug by other known methods. Another potential FDA approved pharmaceutical Nuedexta® (dextromethorphan HBr and quinidine sulfate), is being used to target symptoms of pseudo-affect, which is a condition categorized by unpredictable and sudden episodes of crying or laughing seen in people with ALS [66].

There are several drugs undergoing phase II clinical trials. While there is no cure, there is hope that we are getting closer to mitigating this terrible disorder.

Respiratory Management

In ALS patients, respiratory symptoms such as dyspnea and orthopnea occur due to progressive weakness of the diaphragm and accessory muscles. Vital capacity is one of the most common clinical measures to monitor respiratory function. Other such measures include nocturnal pulse oximetry, arterial blood gases, polysomnography, maximal inspiratory pressure/maximal expiratory pressure, transdiaphragmatic pressure (Pdi), or sniff nasal pressure. Proactive management of respiratory symptoms has a positive impact on both quality of life and survival of ALS patients. Respiratory management mainly depends on non-pharmacological interventions such as non-invasive ventilation, insufflator/exsufflator (also referred to as a cough assist device), nebulizers and portable suction machines. Preventing respiratory infection by maintaining aspiration precautions, good pulmonary hygiene and obtaining necessary immunizations are a crucial part of the strategies for respiratory management in ALS [67].

Nutritional Management

Nutritional status is one of the prognostic risk factors in ALS. Dysphagia and arm weakness are major obstacles in maintaining adequate nutrition, to which anxiety, depression and constipation act as additional factors. Strategies for nutritional management include increasing caloric intake and spreading awareness on safe techniques in swallowing. With progressing dysphagia, weight loss and malnutrition becomes evident which necessitates application of enteric feeding such as percutaneous endoscopic gastrostomy (PEG) or radiologically inserted gastrostomy. However

when vital capacity is below 50%, PEG placement may become unsafe. Hence, placement is generally recommended in patients with dysphagia when the vital capacity is above 50% [68].

Exercise as a Non-pharmacological Therapeutic Approach

ALS involves the rapid deterioration of motor neurons resulting in severe muscle atrophy and respiratory insufficiency. Exercise training is suggested as a potential approach to reduce ALS pathology, but its beneficial role remains controversial. Clinical studies show that both endurance and resistance training have an advantageous impact on the quality of life of ALS victims but without extending life expectancy. Physical therapy may help to maintain mobility and ease the discomfort of muscle stiffness, cramps and fluid retention, thus maximizing existing capabilities and slowing further loss of motion.

Conclusion

ALS is a compilation of multifaceted clinical manifestations with progressive death of neurons resulting in upper and lower motor neuron damage with age. It initiates with primary lateral sclerosis, and in about 3-4 years it can progress to ALS involving muscular atrophy and denervation. Sporadic ALS or sALS accounts for majority of ALS cases across the globe with prevalence found in males. Research into various biomarkers are necessary to facilitate the detection of the pathophysiology of disease. There are therapeutics like Riluzole and Edaravone which can reduce the progression of the disease, but there is no cure. Both early diagnosis and prognosis are required to address this debilitating and chronic neurodegenerative disease.

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