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Amyotrophic Lateral Sclerosis

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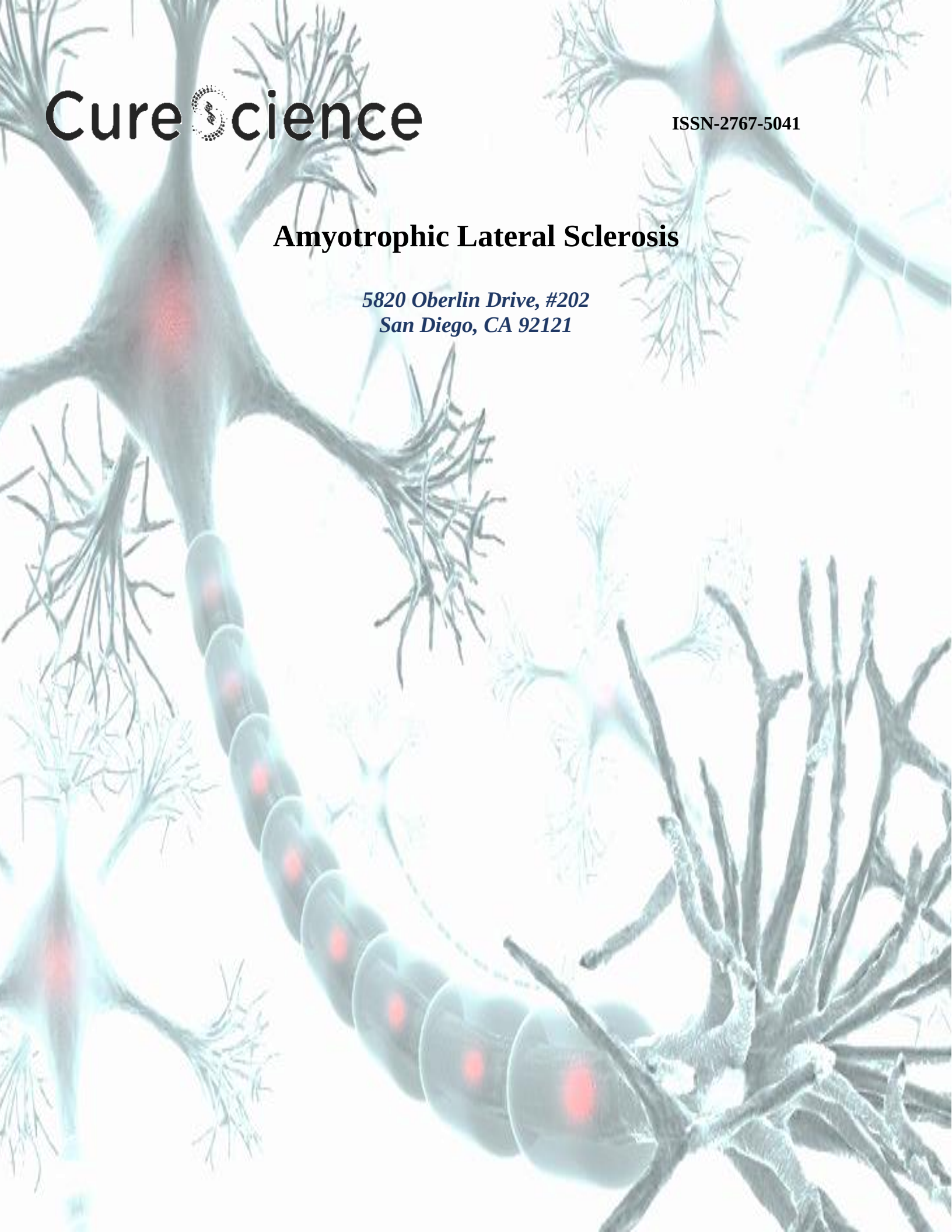

Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting motor neurons. It is unclear what causes ALS, but recent research suggests that multiple complex factors contribute to the death of motor neurons. There is no conclusive identification of specific risk factors for ALS, but ongoing research is exploring whether genetics and/or environmental factors play a role. This progression degeneration leads to muscular atrophy and the cessation of control of voluntary movements. Currently, approximately 30,000 Americans have been infected 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, with 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 those in females. The 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 the gene *C9ORF72.* Another 12-20% of familial cases are caused by mutations in the gene that provides instructions to produce the enzyme copper-zinc superoxide dismutase 1 (*SOD1*). Considering other genetic risk factors for ALS, patients with genotype *UNC13A* may be susceptible to getting the disease. Environmental factors that may contribute to ALS include smoking, body weight, physical activity, exposure to certain chemicals, head injuries, and specific viral infections. To diagnose ALS, doctors typically look at a person's medical history, do a physical exam, perform electrodiagnostic tests, and use neuroimaging. If there is a family history of ALS, genetic testing for the most common mutated genes (C9orf72, SOD1, TDP43, FUS, and TBK1) is advised. Since there is no cure for ALS, treatment focuses on managing symptoms and providing proper care, including support for breathing, nutrition, and exercise.

Introduction

Amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease, is a heterogeneous neurodegenerative disease affecting primarily both upper motor neurons and 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. 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 lower motor neurons. Due to the subsequent loss of function, the muscles gradually become weak and twitch (called fasciculations; see 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. "Limb-onset" ALS occurs when symptoms appear in the arms or legs. Other individuals first notice speech or swallowing problems, termed "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. These symptoms are defined as:

- Dysarthria: Dysarthria is a speech disorder that results from weakness or difficulty in controlling the muscles used for speech. It can cause slurred speech, difficulty pronouncing words, and problems with articulation.

- Dysphagia: Dysphagia is a condition characterized by difficulty in swallowing. It can make it challenging to move food or liquid from the mouth to the stomach and may result in choking, coughing, or aspiration (food or liquid entering the airway).

- Dysphonia: Dysphonia is a voice disorder that affects the quality, pitch, or volume of the voice. It can lead to changes in the sound of the voice, hoarseness, or difficulty in speaking.

- Masseter Weakness: Masseter weakness refers to a reduction in the strength or function of the masseter muscle, which is one of the jaw muscles responsible for chewing. This can affect a person's ability to chew and can be caused by various conditions or neurological issues.

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% of patients develop concomitant behavioral variants of frontotemporal dementia (FTD), while 35%–40% show mild behavioral and/or cognitive changes [2, 3]. 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 neurodegenerative disorders, namely ALS and FTD [5].

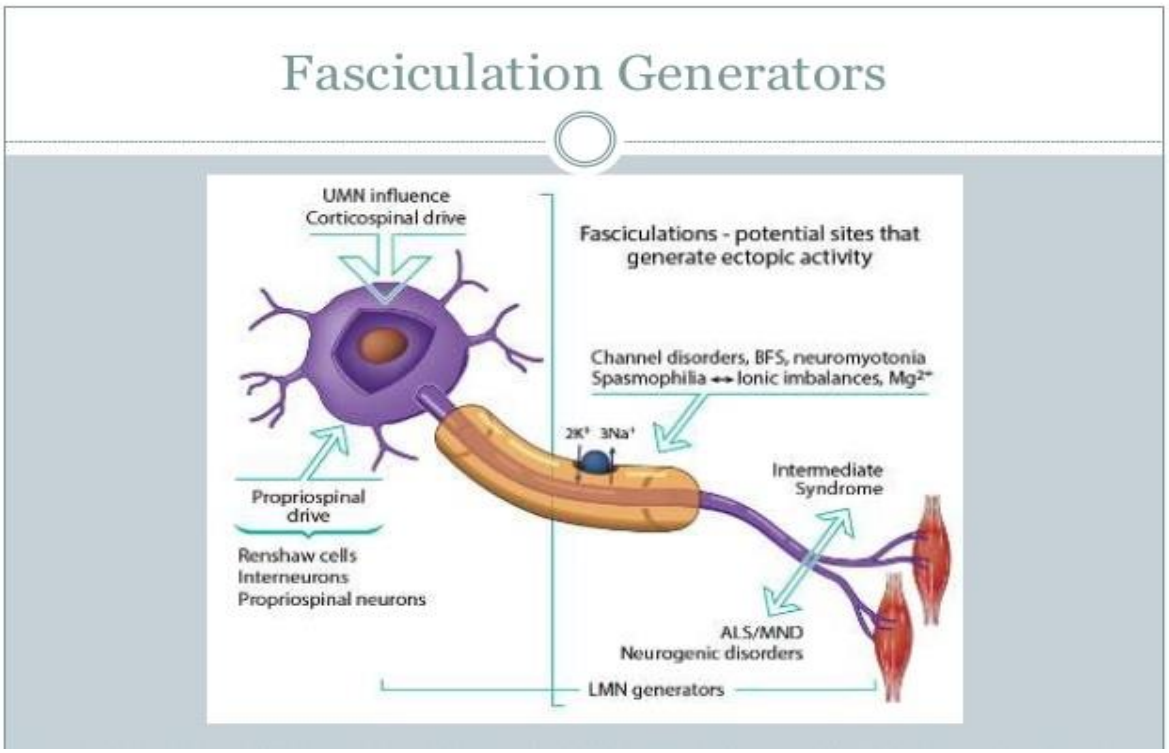

Figure 1: **Fasciculation Generators** (Reference no. [1])

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. Incidence represents the rate of new cases of a characteristic in a population during a specific timeframe, while prevalence is the proportion of the population with a specific characteristic at a given time, regardless of when they are initially acquired it. Both ALS incidence and prevalence in 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 in 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 [1, 7 8, 11].

Types of ALS

Sporadic ALS (sALS):

Most ALS cases (about 90%) are considered sporadic, meaning they appear to happen randomly without any family history of the disease. However, the relatives of people with sporadic ALS are at a slightly higher risk of getting the disease, even though it does not run in their family.

Familial ALS (fALS):

Only a small percentage (around 5-10%) of all ALS cases are inherited, which means they are passed down from parents. In familial ALS, usually, just one parent carries the gene responsible for the disease. Mutations in several genes can lead to familial ALS. A specific gene called "chromosome 9 open reading frame 72," or C9ORF72, is responsible for a significant portion of familial cases (and a small number of sporadic cases). Interestingly, the same mutation can cause damage to certain parts of the brain, leading to a condition known as frontal-temporal lobe dementia (FTD). Some people with this mutation may show signs of both ALS and FTD. Another portion of familial cases is caused by mutations in a gene that provides instructions for making an enzyme called copper-zinc superoxide dismutase 1 (SOD1).

Etiology

ALS is influenced by a combination of genes, the environment, and age-related changes. Researchers have found more than 20 genes connected to the disease, and they are still studying this phenomenon. In families with no history of ALS, genes are estimated to play a role in 30% to 60% of cases. If you have a close family member with ALS, your risk of getting it also goes up [13].

Autosomal dominant causes of ALS

In 1993, the first gene associated with ALS, called SOD1, was identified. Mutations in SOD1 are responsible for approximately 20% of familial ALS (fALS) cases and 1%-2% of sporadic ALS (sALS) cases. These mutations result in the accumulation of abnormal proteins, which disrupt the

normal functions of cells in ALS [15, 18-22]. have mutations in only one of these genes, suggesting multiple genes can contribute to the disease [23, 24].

Risk factorsIn terms of ALS genetic risk factors, the UNC13A genotype is associated with risk [25] and having a mutation in the ATXN2 gene also raises the risk of ALS [26, 27]. ALS risk is higher with older age and being male. Additionally, smoking, body weight, physical activity, exposure to certain substances at work or in the environment, head injuries, and specific viral infections have been suggested as environmental risk factors for ALS [28–30]. However, the exact connection between these factors and ALS is still not fully understood.

Pathogenesis

ALS is a disease where nerve connections break, nerve cells die, and there is also a reaction from certain cells in the brain and spinal cord. We see unusual structures in the remaining nerve cells. To figure out how the disease works and develop new treatments, we need to understand why nerve cells break down in ALS. Mutations in the SOD1 gene have been linked to ALS for more than 20 years, but we still do not fully understand how they cause nerve damage. Scientists think that it is not just one thing, but a combination of factors that lead to nerve cell damage in ALS, suggesting that there might be multiple causes for the disease (Figure 2).

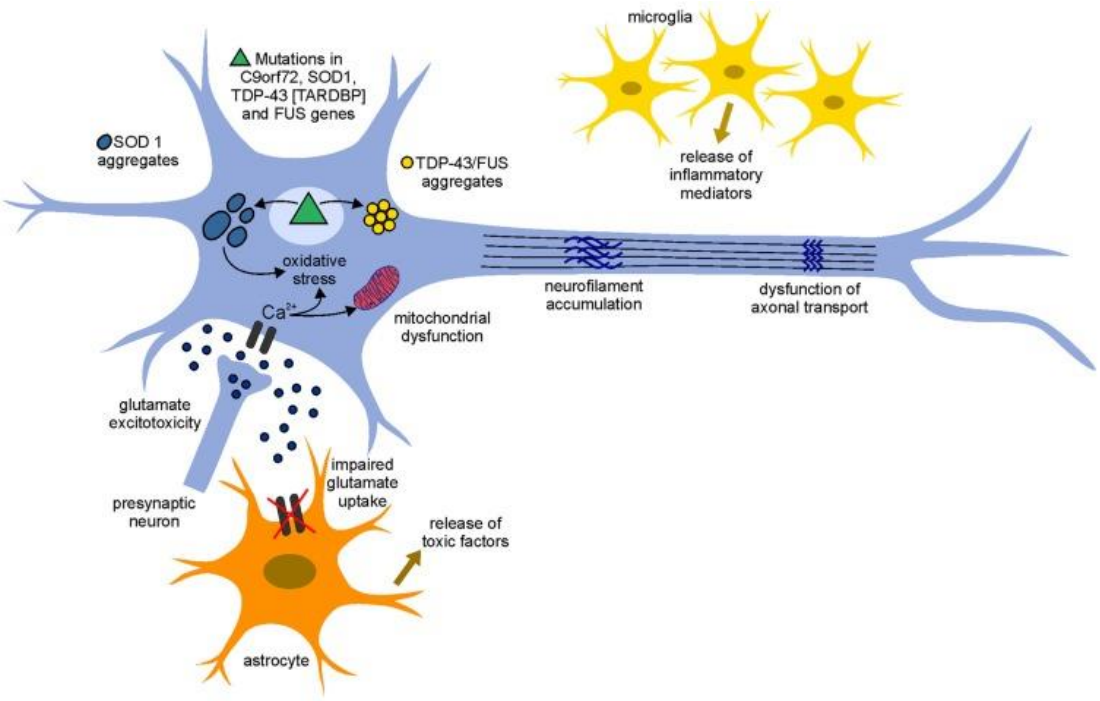

Figure 2. **Pathogenesis involved in amyotrophic lateral sclerosis (ALS)** (Reference no. [69])**.**

Mitochondrial Dysfunction

In ALS, damaged mitochondria are a significant issue. This damage occurs due to reactive oxygen species (ROS) and various changes in cell structure and metabolism. This affects nerve cells, particularly in the spinal cord and muscle cells, in both sporadic (sALS) and familial (fALS) ALS cases, as well as in animal models. Mutated SOD1 protein, found in ALS patients and mice, can disrupt mitochondrial function. It also reduces the activity of key respiratory chain complexes, which affects energy production. Furthermore, the presence of mutated SOD1 in ALS leads to a loss of calcium-binding proteins in motor neurons, making them more sensitive to excitotoxicity. Mitochondria play a crucial role in providing energy and maintaining calcium balance at nerve cell connections. If mitochondria cannot effectively cover these areas, it can lead to metabolic issues and cell death [31 – 37].

Glutamate Excitotoxicity

Glutamate is a chemical messenger in the brain and spinal cord that helps nerves communicate. It is important for normal brain function. However, too much glutamate in the brain can be harmful and may damage nerve cells. There are proteins in the brain, like EAAT2, that usually help control glutamate levels to keep them safe. In some cases, like ALS, these proteins might not work

properly, and glutamate levels get too high, causing harm to nerve cells and leading to disease progression [38 – 41].

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 called oxidative stress. The accumulation of ROS causes irreversible damage to the cell and 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 research suggested that in ALS, a protein called SOD1 could not only lose its normal function but also gain a harmful function. One idea is that mutant SOD1 might change and create damaging molecules called superoxide. These harmful molecules can damage cells. ALS patients have higher levels of these damaging molecules in their body fluids, like cerebrospinal fluid and blood. All these factors could be connected in how ALS develops [42 – 47].

Protein Aggregates

Protein aggregates are clumps of proteins that are folded incorrectly. These clumps can build up around nerve cells and harm them. In ALS, these clumps often contain a mutated SOD1 protein. This protein clumping prevents the proteins from being broken down and leads to the formation of these clumps. These clumps also include other mutated proteins like TDP43 and FUS, which are normally in the cell's nucleus but end up in the cytoplasm, leading to more clumps. All of this together is a significant reason for the death of motor neurons in ALS [48 – 50].

Accumulation of Neurofilaments

The 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 the formation of NF aggregates in ALS is still unclear. The abnormal organization of NF is an important part of the pathogenesis of ALS; however, the exact relationship between its accumulation and motor neuron degeneration remains unclear [52].

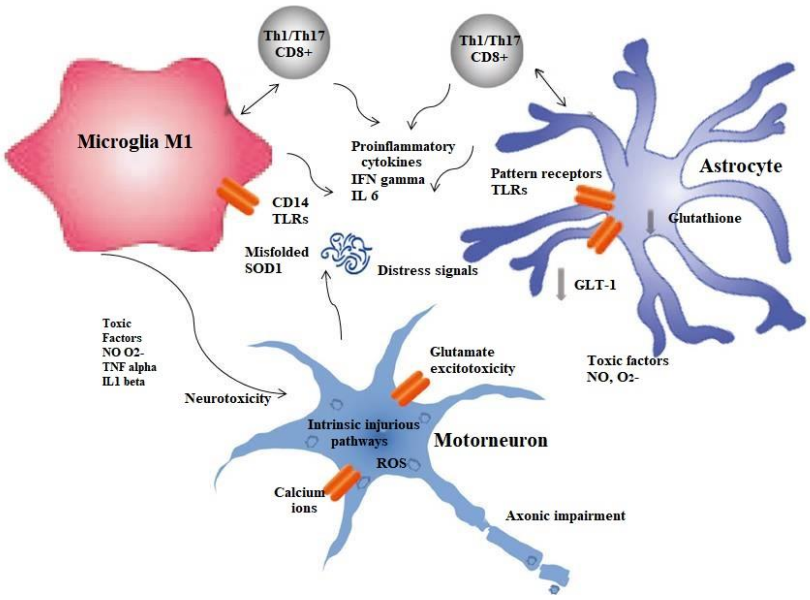

Figure 3. **Cytotoxic phase of Neuroinflammations in amyotrophic lateral sclerosis (ALS**) (Modified from Reference [70]).

Neuroinflammation

In ALS, there is a process where the brain and spinal cord becomes inflamed, with special cells called microglia and astrocytes becoming very active around damaged nerve cells. Even healthy nerve cells can get affected when they are surrounded by these overactive glial cells. Changing the damaged glial cells to healthy ones can slow down the disease in mice.

In the beginning, these glial cells try to protect the nerve cells. But as the mutations worsen the environment, the nerve cells and astrocytes release toxins that cause the microglia to go from being protective to being harmful. This process leads to more inflammation and harms the nerve cells, making the disease worse [53, 54, 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

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 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 the hypothenar muscles, a characteristic that is referred to as the split-hand syndrome [55].

As noted above, different muscles are affected at different times. At the start, the muscles between your hand bones are affected, making finger extenders weaker than finger flexors. As the disease progresses, leg muscles are affected, with the front thigh muscle being the first to weaken, followed by the calf muscle, and then the muscles at the back of the thigh before the front thigh muscles.

People with bulbar ALS usually first have trouble speaking clearly or swallowing, and sometimes their voice may sound odd. They may also have trouble closing their mouth or chewing. In the later stages, muscles around the neck and head weaken, leading to difficulty holding up the head or keeping a straight posture. Some people with ALS may also have episodes of uncontrollable laughter or crying. In a few cases, muscle twitches, cramps, or mild weight loss may happen before muscle weakness [56, 57]. A neurological examination of patients with classic ALS shows a combination of signs of upper motor neuron (UMN) and lower motor neuron (LMN) involvement. Signs in the lower part include muscle weakness, shrinking, muscle twitches, and floppy muscles. Upper part signs include overactive reflexes, tense muscles (especially in the arms and legs), and slow movements (especially in tongue movement). Most patients start with problems in their spine or throat. Recent research shows that there are different causes of ALS, making it a disease with various symptoms, not just in the muscles but also in the brain. This results in different ways the disease shows up and progresses. So far, there are no widely agreed-upon rules to categorize the different phenotypes of ALS (Figure 4). Phenotype includes observable traits like height, eye color, and blood type, and it is influenced by both genetics (genotype) and the environment. ALS can cause muscle problems, like weakness and twitches, in the body's lower parts, and make muscles floppy. In the upper parts, it can lead to tense muscles, overactive reflexes, and slow movements. Most people with ALS initially have issues with their spine or throat. Recent research

has found that there are various causes of ALS, resulting in different symptoms, not just in the muscles but also in the brain [58 – 60].

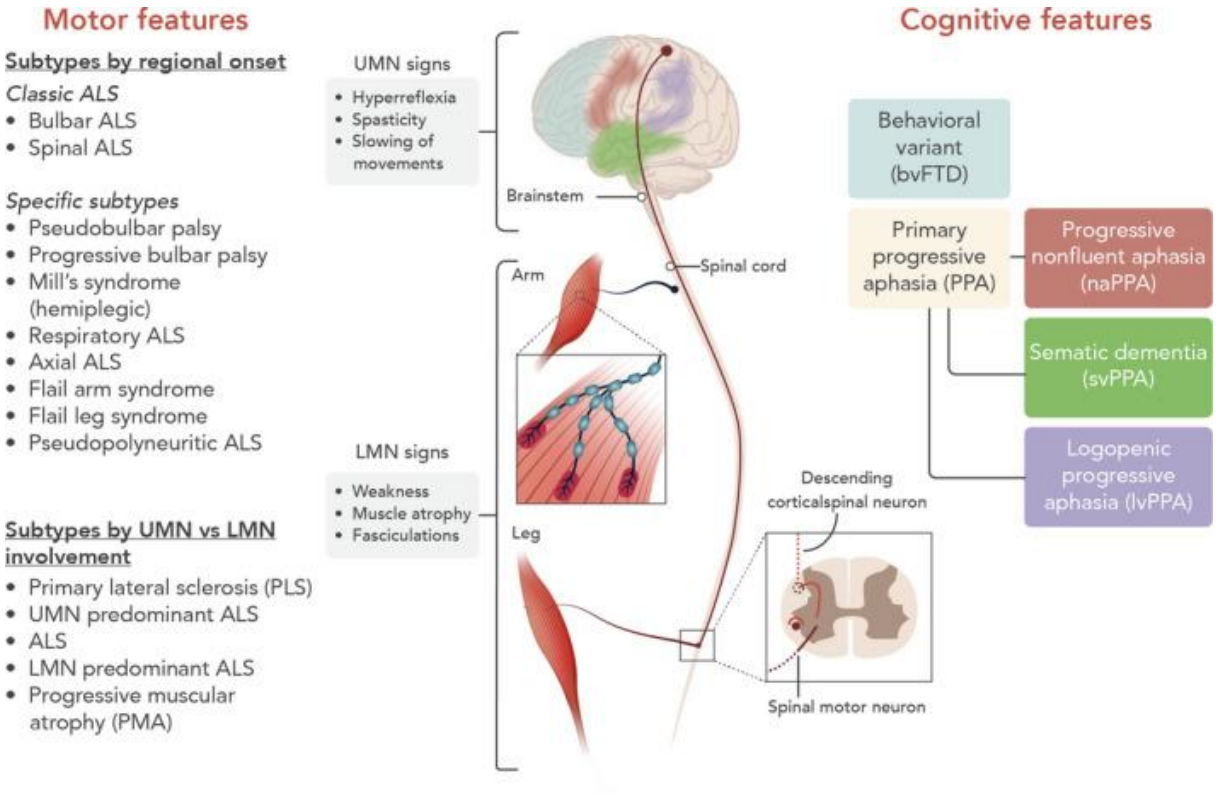

Figure 4. **Clinical presentations of ALS** (Reference no. [1])

Diagnosis

ALS may be diagnosed based on 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 that are sharp [61]).

Biomarkers play a crucial role in diagnostic, prognostic, and predictive research studies. Although it has not yet been established as a standard clinical practice, several biomarkers such as

cerebrospinal fluid neurofilament levels 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, or cervical myelopathy [62, 63]. In specific cases, brain and spinal cord magnetic resonance imaging is performed to exclude structural lesions affecting the motor system. Furthermore, ^{18}Ffluorodeoxyglucose (^{18}FFDG) positron emission tomography may be 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, and TBK1). But there is as yet no consensus on genetic testing for patients with sALS. However, doctors advise genetic testing only when genetic counseling 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 are the only treatments. The current FDA-approved drugs are Riluzole and Edaravone. Although these medications cannot reverse or stop the progression of ALS, they can provide symptomatic benefits [66]. A report suggested from randomized clinical trial data on Riluzole showed 35% improved twelve-month survival rates and were 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 intravenous administration. A survey revealed 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; and 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 characterized 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 used 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 positively impacts the quality of life and survival of ALS patients. Respiratory management depends on non-pharmacological interventions such as non-invasive ventilation, insufflator and exsufflator (also referred to as cough assist devices), nebulizers, and portable suction machines. Preventing respiratory infection by maintaining aspiration precautions, good pulmonary hygiene, and obtaining necessary immunizations is 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 to maintaining adequate nutrition, to which anxiety, depression, and constipation add additional factors. Strategies for nutritional management include increasing caloric intake and spreading awareness about safe swallowing techniques. With progressing dysphagia, weight loss and malnutrition become evident, which necessitates the application of enteric feeding techniques 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 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 reducing 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 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

Amyotrophic lateral sclerosis (ALS) presents a complex array of clinical manifestations, characterized by the progressive degeneration of neurons, leading to damage in both upper and lower motor neurons as individuals age. The disease typically commences as primary lateral sclerosis and, over about 3-4 years, may evolve into full-blown ALS, marked by muscular atrophy and denervation. Sporadic ALS, or sALS, stands as the predominant form of ALS cases globally, with a notable predilection for males. Advancing our understanding of the ailment's pathophysiology necessitates intensive exploration of various biomarkers.

While therapeutics such as Riluzole and Edaravone can slow the disease's progression, a definitive cure remains elusive. Timely diagnosis and an accurate prognosis hold paramount importance in addressing this devastating and persistent neurodegenerative condition.

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