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Amyotrophic lateral sclerosis: A clinical review

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Abstract

A neurodegenerative disease of the motor pathways, amyotrophic lateral sclerosis (ALS) always results in death within a few years of start. 10% of ALS cases are familial variants of the illness (FALS), while the majority of ALS cases are sporadic. More than 20 genes have been connected to FALS since the 1990s, when a causal gene was initially discovered, and thanks to current developments in genetics. Both proximally and distally in the upper and lower limbs, localized muscular weakness and wasting are symptoms that are present in about two-thirds of people with typical ALS who have the spinal form of the disease (limb onset). Spasticity may gradually develop in the weaker atrophic limbs, impairing walking and manual dexterity. Most patients with bulbar onset ALS will experience symptoms in the limbs within 1-2 years after developing bulbar symptoms, which often include dysarthria and dysphagia for solids or liquids. Although the exact causes of amyotrophic lateral sclerosis are unknown, numerous environmental risk factors and several genes that have been found to contain disease-associated mutation are among them. The nature, epidemiology, genetic correlations, and environmental exposures linked to amyotrophic lateral sclerosis are reviewed here. Although the exact causes of amyotrophic lateral sclerosis are unknown, numerous environmental risk factors and several genes that have been found to contain disease-associated mutation are among them. The nature, epidemiology, genetic correlations, and environmental exposures linked to amyotrophic lateral sclerosis are reviewed here.

Keywords: Amyotrophic lateral sclerosis; Sporadic and familial ALS; Risk factors; Genetics; Environment factors

1. Introduction

A deadly neurological illness with an unclear cause, amyotrophic lateral sclerosis (ALS) is marked by progressively worsening paralysis that eventually results in death three to five years after the onset of symptoms. When several population-based registers were set up to prospectively ascertain the incidence of ALS in specific geographic areas in the early 1990s, the field of ALS epidemiology reached a mature state [1]. Patients and health systems are subjected to a significant clinical and financial burden from neurodegenerative disorders. Disease heterogeneity and the existence of overlapping phenotypes have hindered the development of disease-modifying treatments and effective palliative care interventions [2]. Amyotrophic lateral sclerosis (ALS), the most prevalent adult form of motor neuron disease, causes progressive degeneration of motor neurons in the spinal cord, brainstem, and cortex, resulting in paralysis and respiratory failure three to five years after the onset of symptoms [3]. Lou Gehrig's disease, commonly referred to as ALS, is a debilitating neurological illness that strikes adults and has no known cure1. Our understanding of the causes is still limited. About 10% of cases have a first or second-degree relative with ALS (familial ALS, or FALS), while the disease is primarily sporadic (SALS). About 20% of FALS cases have mutations in SOD1, which codes for Cu/Zn superoxide dismutase, for a total frequency of about 2%. Even more uncommon genes have been found to cause ALS illness. Finding novel and possibly prevalent genetic risk factors for ALS will help develop biomarkers, advance our understanding of the illness, and inspire creative new therapies [4]. Numerous genetic investigations have been

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conducted on ALS, but the only reliable results have been the identification of six genes SOD1, TARDBP, FUS, VAPB, ANG, and OPTN where mutations predispose to ALS, both in familial and sporadic cases, and account for around 2% of all cases of ALS. Although a big study was successfully replicated in a second large internal cohort, genome-wide association studies have not produced independent replication of findings. However, it is believed that all cases of ALS include a hereditary component. By enabling an assessment of ALS heredity, twin research would assist in determining if this assumption is plausible [5]. Muscle weakness, twitching, and cramping are the most prevalent signs of both forms of ALS, and they can ultimately result in muscle dysfunction. Patients with ALS will have dysphagia and dyspnea in the most advanced stages [6].

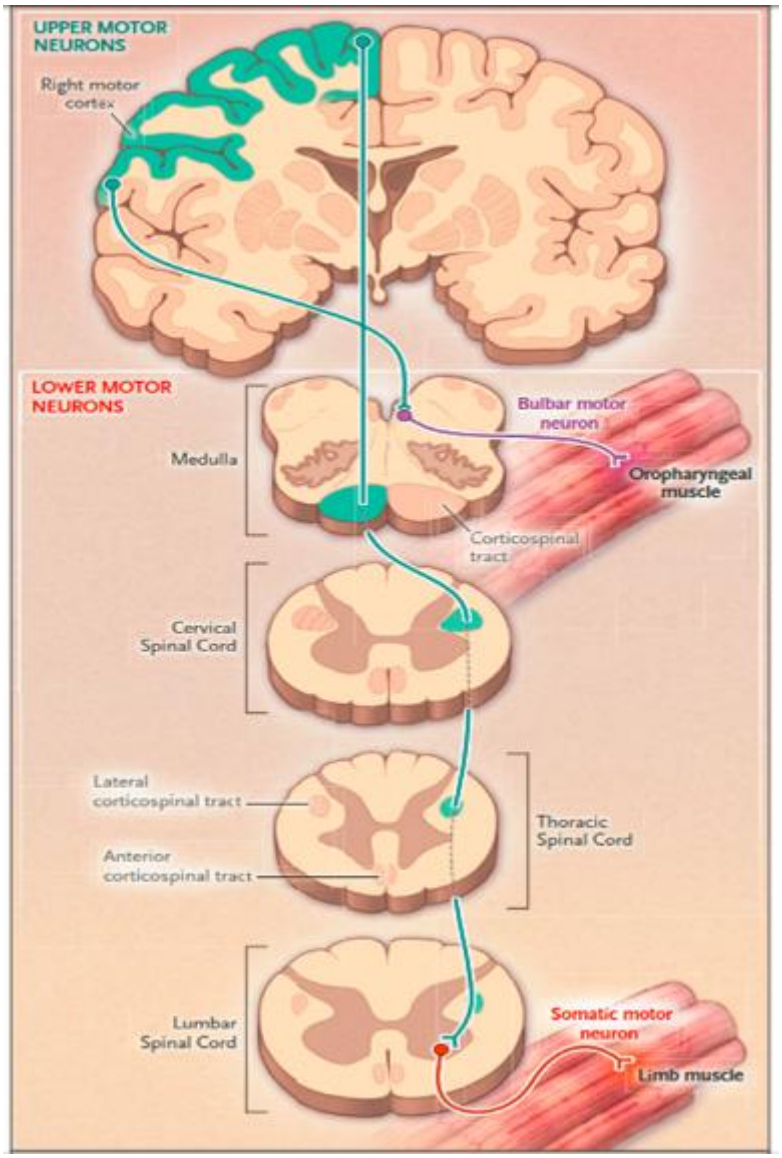

Figure 1 The Motor System

The motor system is composed of corticospinal (upper) motor neurons in the motor cortex and bulbar and spinal (lower) motor neurons, which innervate skeletal muscle [7].

The progressive paralytic disease known as amyotrophic lateral sclerosis (ALS) is typified by the loss of motor neurons in the brain and spinal cord. Focused weakness is the first symptom, but it gradually extends to affect most muscles, including the diaphragm. Respiratory paralysis usually results in mortality within 3 to 5 years. Lower motor neurons innervate muscle, while higher motor neurons are found in the motor cortex and lower populations in the brain stem and spinal cord (Fig. 1). The failure of corticospinal (upper) motor neurons causes spasticity and rigidity in the muscles. Affected lower motor neurons first exhibit excessive electrical excitability, which causes "fasciculations," or spontaneous muscle twitches; as they degenerate, they lose synaptic contact with their target muscles, which causes

them to atrophy. About one-third of ALS cases are bulbar, characterized by difficulties speaking, eating, or chewing. ALS usually starts in the limbs. Neurons that innervate the eye and sphincter muscles are spared in ALS until the disease is advanced. Clinical examination along with electromyography to confirm the degree of denervation and laboratory tests to rule out reversible illnesses that may resemble ALS are the main methods used to make the diagnosis [7].

According to the second meaning, ALS is a particular type of motor neuron disease that manifests symptoms in both the upper and lower motor neurons. Muscle atrophy, weakness, and fasciculation that indicate a disorder of the lower motor neurons are referred to as "amyotrophic." The term "lateral sclerosis" describes the hardness to palpate lateral spinal cord columns in postmortem specimens, where gliosis occurs after corticospinal tract degeneration. Upper motor neuron symptoms include clonus, Babinski signs, Hoffmann signs, and hyperactive tendon reflexes. Progressive spinal muscular atrophy is the term used to describe the disorder if lower motor neuron symptoms are the only ones visible. Only upper motor neuron symptoms are present in primary lateral sclerosis. Because anomalies in both upper and lower motor neurons are likely to be found at autopsy, these disorders are regarded as variations of ALS [8]. The elements of ALS that contribute to disease heterogeneity will be reviewed in this primer, along with the prospects for novel therapeutic trials that consider the most recent developments in our knowledge of this disease spectrum. Determining disease pathways that can be targeted by drugs and identifying patient subgroups that are likely to respond to these novel therapeutic agents present challenges for new therapeutics [9].

2. Epidemiology

The higher incidence of spinal-onset ALS in men is primarily responsible for this discrepancy. In contrast to other neurodegenerative illnesses, such as Parkinson disease and Alzheimer disease, the chance of acquiring ALS peaks between the ages of 50 years and 75 years and falls thereafter. This characteristic implies that ALS is a disease for which age is one of many risk factors rather than a disease of aging. The adjusted age-specific incidence of the disease is not rising, according to a thorough analysis of populations spanning more than ten years [10]. In most cases, the cause of amyotrophic lateral sclerosis (ALS) is still unknown. By examining potential risk variables and describing illness burden, epidemiologic studies can provide a foundation of evidence for future mechanistic research. The purpose of this study was to present an overview of epidemiologic studies that examined the incidence and risk variables of ALS that were published during the last 18 months [11].

Degenerative alterations to both upper and lower motor neurons are hallmarks of the deadly motor neuron disease (MND) amyotrophic lateral sclerosis (ALS). Signs and symptoms include increasing weariness, swallowing difficulties, and progressive muscle atrophy and weakening, which usually result in respiratory failure and death. Overall loss of independence is the result of progressive functional deficiencies. Only 5–10% of individuals survive for more than ten years; the median survival is two to four years from beginning [12]. Our knowledge of additional risk factors is less developed, even though we are constantly learning more about the genetic foundation of ALS. Other factors, such time and environmental exposures, must underlie or impact disease vulnerability because ALS develops most frequently in adults, even though its genetic causes are established from conception. However, little is known about the connections between environmental factors, genetic risk, and disease phenotype. The identification of environmental risk factors for ALS has proven challenging, partly since exposure to these factors might vary over time and may not be appropriately documented. Suspected risk factors for ALS include smoking, military service, b-N-methylamino-L-alanine, head trauma, electromagnetic fields, agricultural chemicals, exposure to lead and other heavy metals, and athletic propensity or activity, even though there are currently no known environmental risk factors that are unquestionably linked to the disease. Gene abnormalities are only one of numerous processes that ultimately contribute to ALS, according to the gene-time-environment model, which proposes that ALS develops across a number of steps [13].

2.1. Cognitive & behavioral changes in ALS

Certain types of ALS are characterized by inherent behavioural and cognitive changes. The current strategy is to screen for cognitive and behavioural abnormalities after making a clear diagnosis of ALS. According to studies, FTD affects 5–15% of ALS sufferers. Certain types of ALS are characterized by inherent behavioural and cognitive changes. The current strategy is to screen for cognitive and behavioural abnormalities after making a clear diagnosis of ALS. According to studies, 5–15% of ALS patients also have FTD, and up to 50% of them exhibit cognitive or behavioural abnormalities that fall within the FTD spectrum. Similarly, modest motor neuron involvement is observed in about 40% of FTD patients, and ALS develops in 12.5% of by-FTD patients [14]. The idea that ALS is a worldwide neurodegenerative illness that falls on the same continuum as FTD is supported by these behavioural and cognitive alterations. About 50% of FTD cases and approximately 97% of ALS cases have transactive response DNA binding protein (TDP)-43 proteinopathy, an almost universal clinical characteristic of ALS. TDP-43 disease in non-motor brain areas pertaining to executive

function, language, and fluency has 100% specificity for mild impairments in these domains. Cognitive impairment is strongly predicted by certain patient characteristics, such as bulbar onset and C9 or f72 status, which may assist the patient and doctor predict this problem. Moreover, behavioural abnormalities and cognitive dysfunction might predict the stage of the disease [15].

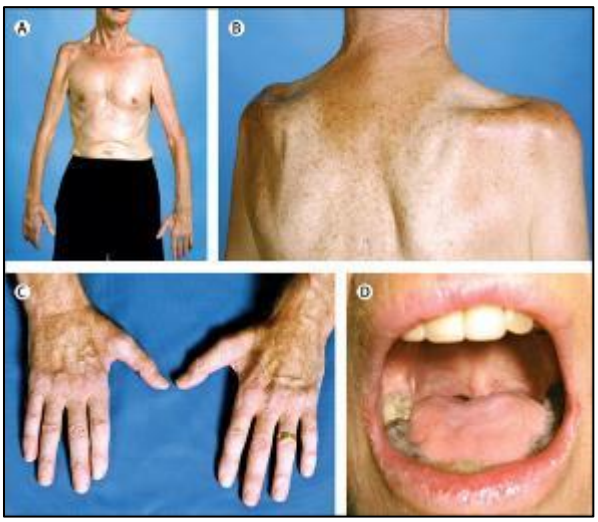

Figure 2 Clinical features of muscles wasting in a patient with ALS [16]

2.2. Amyotrophic lateral sclerosis phenotypes

2.2.1. Classic phenotype

With a men-to-women rate ratio of 1.65:1, this is the most prevalent ALS phenotype in males and the second most prevalent in women. The age-specific incidence rate peaks in the seventh decade for both genders, and its onset age is 62.8 years (SD 11.3). FTD is present in 4% of individuals with this characteristic. It has a 10-year survival rate of 13.0% and a median survival duration of 2.6 years [16].

2.2.2. Bulbar phenotype:

The incidence of bulbar ALS is the same in both sexes (1/100,000 population), with a 0.98:1 male to female rate ratio. For both genders, the age-specific incidence rate peaks in the eighth decade. FTD, the most common ALS characteristic, affects 9% of bulbar patients. Bulbar ALS has the second-worst median survival time (2.0 years); only 3.4% of patients made it to the 10-year mark [17].

2.2.3. Pyramidal phenotype

Patients with this phenotype are relatively young at onset (58.3 years), genders are equally represented (men to women rate ratio of 1.04:1), the age-specific incidence rate peaks in the 7th decade (Figure 1E), FTD is relatively rare (2.5%), the median survival time is 6.3 years, and the 10-year survival rate is 31.9% [18].

2.2.4. Respiratory phenotype:

With an annual incidence rate of 0.06/100,000 for men and 0.01/100,000 for women, this is the rarest phenotype. No patient with this phenotype lived for more than ten years, and its median survival duration is 1.4 years [18].

3. Pathogenesis of ALS:

It is thought that several interrelated pathophysiological processes that lead to extensive network disruption cause motor neuron damage in ALS. The fact that ALS is heterogeneous implies that different pathways may be more or less important in each patient. To represent this complexity, preclinical disease modelling must advance. Upstream targeting of the initiating factor (e.g., by gene silencing or gene replacement) and one or more medications that improve several aspects of the disease pathophysiology could be beneficial strategies for developing neuroprotective therapeutics [19].

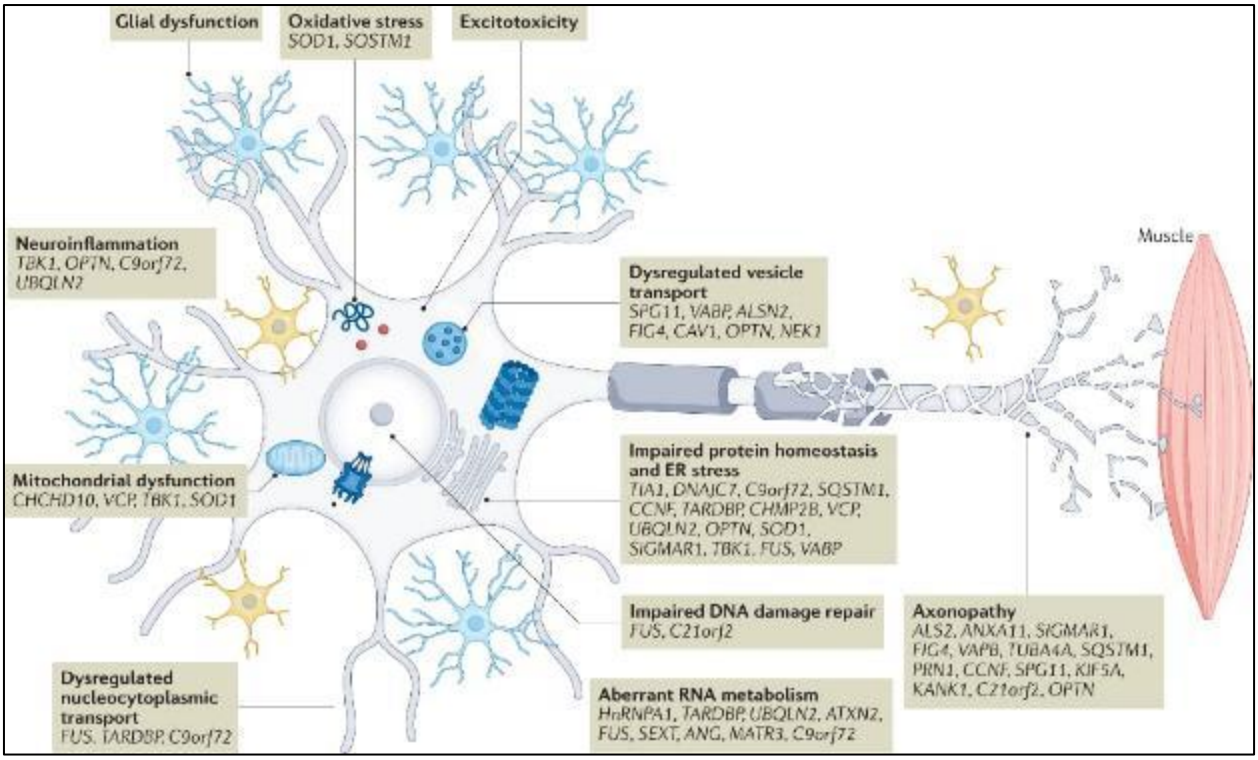

Figure 3 ALS pathophysiology, genetic causes and risk factors [19]

3.1. Genetic factors:

More and more genes are being identified as linked to and responsible for ALS. The most prevalent ones are FUS, SOD1, TARDBP, and C9 or f72. Protein and RNA metabolism are two frequently suggested pathogenic pathways [20]. Mutations in the Copper-Zinc superoxide dismutase (SOD1) gene are found in 2% of patients with SALS and 20% of cases of autosomal dominant FALS. Instead of impairing the antioxidant action of the SOD1 enzyme, mutations in the gene are believed to cause disease by producing a harmful increase of function. Als in (ALS2), sena toxin (ALS4), vesicle associated membrane protein (VAPB, ALS8), angiogenin, and a mutation in the p150 subunit of dynactin (DCTN1) are other genes that cause familial MND. Mutations in the TARDBP gene, which codes for the TAR-DNA binding protein TDP-43 and is found on chromosome 1p36, have recently been connected to both sporadic and familial ALS [21].

3.2. Oxidative stress:

Excess reactive oxygen species (ROS), reactive nitrogen species, or compromised antioxidant defence systems can all lead to oxidative stress. ROS alter the structure and function of biomolecules such as proteins, lipids, DNA, and RNA, which greatly contributes to neuronal damage and the aging of the central nervous system (CNS). Numerous pieces of evidence suggest that oxidative damage plays a significant part in the pathogenesis of ALS. Both human ALS bio samples and ALS models have been shown to exhibit altered oxidative stress biomarker profiles. Glutathione homeostasis and the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant response element (ARE) cytoprotective system are two more oxidative stress defence systems that have been shown to be compromised in ALS [19].

3.3. Excitotoxicity:

This term describes the damage to neurons caused by excessive glutamate-induced activation of postsynaptic glutamate receptors, including AMPA and NMDA receptors on the cell surface. It is believed that this excessive glutamate receptor stimulation causes a huge calcium influx into the neurons, which raises the production of nitric oxide and ultimately causes neuronal death. Some ALS patients have higher glutamate levels in their CSF. The depletion of the excitatory amino acid transporter EAAT2 in glial cells has been implicated in this rise [21].

3.4. Mitochondrial dysfunction:

SOD1 transgenic mice, cellular models, and sporadic ALS patients have all been shown to exhibit abnormalities in mitochondrial architecture and biochemistry. Reduced activity of respiratory chain complexes I and IV and increased

calcium levels in mitochondria from ALS patients point to a malfunction in energy metabolism. ALS patients have been found to have mutations in their mitochondrial DNA [21].

4. Genetics and ALS.

With the rate of gene discovery doubling every four years, there are currently over 25 genes with a confirmed connection to ALS. Although thorough genealogy investigations that include more distant relatives and similar diseases indicate that over 20% of people have a relevant family history, up to 10% of persons have a family history of ALS in a first-degree relative. Although the genes causing familial ALS to have been found in roughly 70% of cases, even in people without a family history, there is a sizable genetic component [22]. Even though most ALS cases are intermittent, FALS may account for 5–10% of all ALS cases. However, there isn't always a clear distinction between clinically recognized FALS and SALS, therefore this prevalence might be overestimated (because of the different criteria employed). The genetic diversity and complexity of ALS still require doctors to refer to genetic tests and to accurately identify which genes are likely to be altered, even if large-scale genetic screening becomes more widely available and accessible in ordinary clinical practice [23]. Most ALS genes have varied and age-dependent penetrance and are inherited dominantly. There is notable variation in the age of onset and the course of the disease within and across families. The UBQLN2 gene is X-linked dominant, and other genes that may cause recessive illness include OPTN, SPG11, FUS, and SOD1 (particularly, the homozygous Asp90Ala mutation) [24]. Familial instances may be "apparently" sporadic due to heritability being concealed in tiny pedigrees (death from other reasons prior to the start of ALS, loss of contact, etc.) [14]. Although this term is commonly misunderstood to refer to ALS that develops without a genetic basis, it describes ALS that manifests without a family history of the disease [25]. The first ALS gene, cytosolic superoxide dismutase or SOD1, was reported in 19932, with more than 50 additional potential ALS genes published since, although validating the causality of specific variants remains a challenge [26]. Less often reported causes of ALS include mutations in several different genes, including VCP, PFN1, MATR3, CHCHD10, TBK1, and NEK1. Here, we go over five ALS genes that were discovered after 2018 by whole-exome and whole-genome sequencing; each of these genes offers new information on the pathophysiology of the disease and a fresh avenue for the creation of treatments [27].

5. Amyotrophic lateral sclerosis symptoms: [28,29]

PLS with pure UMN involvement, PMA with pure LMN involvement, bulbar onset ALS, which is characterized by:

Speech and swallowing difficulties followed by limb weakening in later stages of the disease, and limb-onset ALS, which combines upper motor neuron (UMN) and LMN signs in the limbs, are the main categories into which the various ALS phenotypical expressions are divided.

Mild depression, associated with low mood, anhedonia, apathy, and increased irritability.

In the context of multiple problematic symptoms in ALS, pain, breathing and bowel and bladder, while increasing in perceived impact of QOL over time, were not perceived to be as problematic as the other physical symptoms.

Localized muscle weakness in the upper and lower limbs of ALS patients starts either proximally or distally. The symptoms typically start out asymmetrically and proceed to include widespread muscle weakening and atrophy.

Most patients experience respiratory and bulbar symptoms as well as spasticity, which impairs manual dexterity and walking. Emotional instability and excessive yawning are examples of pseudobulbar symptoms that have been noted in a significant percentage of patients.

Significant limb or bulbar symptoms are often absent in approximately 5% of patients with respiratory weakness. Rather, these patients exhibit nocturnal hypoventilation or type 2 respiratory failure, which manifests as dyspnoea, orthopnoea, sleep disturbance, excessive daytime somnolence, morning headaches, anorexia, impaired attention, and mood swings or irritability.

Early during limb-onset ALS, muscular atrophy is typically identified, affecting the proximal thigh or distal foot muscle in the lower limbs as well as the muscles of the wrists, forearms, or shoulders.

Thick mucus that patients are unable to clear because of muscle weakness and an ineffective cough may respond to beta blockers or to guaifenesin or nebulized saline or acetylcysteine, often in conjunction with an insufflation-exsufflation (cough-assist) device.

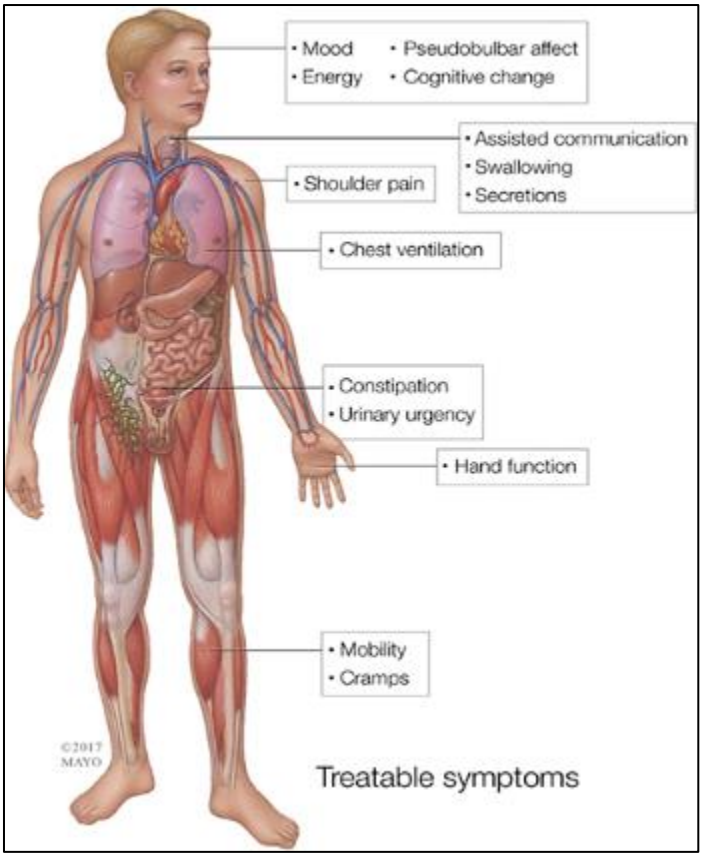

Figure 4 Illustration of symptoms that can be addressed in amyotrophic lateral sclerosis [13]

6. Clinical types and patterns of ALS

6.1. Sporadic ALS

ALS can manifest on its own or coincidentally with other underlying medical conditions [30].

6.2. Genetically determined (familial, hereditary) ALS

If a family history of a dined pathogenic mutation is found, the diagnosis of ALS may be upgraded to Clinically Definite Familial ALS Laboratory supported: ALS presenting with progressive upper and/or lower motor neuron signs in at least one region (in the absence of another cause for the abnormal neurological signs). ALS is a disease that can be inherited in one or more generations and is linked to various modes of inheritance and dined pathogenic mutations, such as hexosaminidase A/B deficiency or mutants of the SOD1 gene. However, the criteria for diagnosing sporadic ALS apply in genetically determined instances when the gene has not been found (even if linkage is demonstrated) [30].

6.2.1. Mutations in Familial and Sporadic Amyotrophic Lateral Sclerosis

Mutations in CuZn superoxide dismutase (SOD1) are known to cause ALS and are detected in ~20% of FALS and 3% of sporadic ALS (SALS) patients. A hazardous increase of function causes selective motor neuron degeneration in mice transgenic with human SOD1 mutants. Chromosomes 18q, 16q, and 20p have been associated with pure FALS kindreds. Chromosomes 9p and 9q have been connected to other dominant kindreds with clinical spectrums ranging from pure ALS to pure frontotemporal lobar dementia (FTLD) and individuals with characteristics of both illnesses; however, no causative mutations have been found in these kindreds [31]. Subject 5's spinal cord, which had the E478G mutation, showed anterior horn cell and corticospinal tract myelin loss [32]. Five percent of people with amyotrophic lateral sclerosis (ALS), a motor neuron disease, self-report having a positive family history of the condition. This is most often a Mendelian autosomal dominant feature. Since 1993, the pathophysiology of ALS has been linked to mutations in more than 36 genes, some of which have been predicted to impair intracellular transport and cytoskeletal function [33].

6.3. Endemic ALS:

Even though the frequency of ALS appears to be decreasing, it is more common in endemic areas. Genetic susceptibility factors are expected to be less significant in endemic ALS, which is believed to be more of an environmental condition. The main cause of motor neuron degeneration is believed to be environmental neurotoxins, such as beta-methylamino-L-alanine (BMAA), which is generated by cyanobacteria and obtained from the food chain [34].

7. Risk factors for ALS.

Although a few factors have been suggested to be linked to ALS, older age, male sex, and a family history of ALS are now the only known risk factors [35].

7.1. Smoking

Because of oxidative stress, inflammation, and the neurotoxicity of heavy metals included in cigarettes, cigarette smoke has been shown to raise the risk of developing ALS. The risk of ALS is greater for active smokers who begin smoking at a younger age. However, it has little to do with how long or how hard a person smokes. Additionally, formaldehyde, which is found in exhaled cigarette smoke, is linked to increased mortality rates in ALS patients. The most reliable nongenetic risk factor for ALS is believed to be cigarette smoking. Lastly, there hasn't been any research done on the positive effects of smoking cessation on ALS patients [6].

7.2. Pesticides

Insecticides, fungicides, herbicides, and rodenticides are the four primary categories of pesticides. Oral, cutaneous, and inhalation exposure to these toxins is common and does not only affect professional farmers. Because they block acetyl cholinesterase, the enzyme that stops acetylcholine's biological function, some of them especially organophosphate pesticides can harm the nervous system. Furthermore, the majority of these substances are recognized for their capacity to cause neuronal death, α-synuclein accumulation, mitochondrial dysfunction, and oxidative stress. The use of pesticides Insecticides, fungicides, herbicides, and rodenticides are the four primary categories of pesticides. Oral, cutaneous, and inhalation exposure to these toxins is common and does not only affect professional farmers. Because they block acetyl cholinesterase, the enzyme that stops acetylcholine's biological function, some of them especially organophosphate pesticides can harm the nervous system. Furthermore, the majority of these substances are recognized for their capacity to cause neuronal death, α-synuclein accumulation, mitochondrial dysfunction, and oxidative stress [36].

7.3. Exposure to Metals

Among all the heavy metals that might be associated with ALS, lead exposure seems to be studied the most possibly due to the ALS-like symptoms experienced by people exposed to high concentrations of lead. Since then, recent studies have found a correlation between lead exposure and ALS. As such, professions related to lead exposures, such as welding, have demonstrated a significant association with developing ALS with odds ratio (ORs) ranging from 1.9 to 5.7 [37].

8. Diagnosis

8.1. Diagnostic guidelines for ALS

According to the following recommendations, the diagnosis of ALS is still based on a clinical evaluation conducted by a qualified medical professional [38]:

- Evidence of UMN degeneration by clinical examination
- Evidence of LMN degeneration by clinical, electrophysiological or neuropathological examination
- Progressive spread of the symptoms within a limb or to other limbs or regions, as determined by patient history or examination
- Lack of electrophysiological or pathological evidence of other disease processes that might explain the patient's symptoms

8.1.1. Essential investigations in patients with ALS [10].

- Blood tests
- Erythrocyte sedimentation rate

- C-reactive protein
- Hematological screen: full blood count
- Liver function tests: alanine transaminase and aspartate transaminase levels
- Creatine kinase
- Creatine
- Electrolytes: Na+, K+, Cl–, Ca2+, PO4
- Glucose
- Lactate dehydrogenase
- Imaging studies
- MRI and/or CT (head and neck, thoracic, lumbar)
- Chest radiography

8.2. Diagnostic criteria

Since there is currently no conclusive test to diagnose ALS, the diagnosis is made by combining evidence of disease progression with clinical investigation to rule out other potential explanations of the presenting symptoms. Accurate and prompt diagnosis can be complicated by the discovery of genetic and pathological subtypes of ALS, the occurrence of phenotypic overlap with other neurodegenerative diseases, and the expanding knowledge of the extra-motor characteristics of ALS [9]. Since there is no trustworthy biochemical sign for ALS, clinical neurophysiologists are heavily involved in the diagnosis process. EMG signals of acute and chronic partial denervation can be used to diagnose abnormalities in lower motor neurons and their distribution [39].

8.3. Potential Biomarkers Identified In Patients With ALS

Receiving an ALS diagnosis can be difficult. It takes an average of 12 months from the onset of symptoms to diagnose this neurodegenerative disease due to the lack of precise diagnostic tools and quantifiable biomarkers [40]. Diagnostic biomarkers are one type of biomarker that can identify or validate the existence of an illness or other condition. It might be possible to identify ALS sooner and enroll individuals in clinical trials or begin treatment at a time when therapies may be more effective if there were effective diagnostic biomarkers for the condition. Given that ALS is a clinically and pathophysiologically diverse disorder, diagnostic biomarkers may also be able to identify and distinguish between ALS subtypes [41].

8.4. Structural MRI

Regional grey and white matter and localized atrophy can be thoroughly analyzed thanks to structural MRI (sMRI) techniques. Three-dimensional images obtained with a resolution of 1 mm in each dimension to guarantee precise structural delineation are typical examples of high-resolution, single-contrast images. Combining several high-resolution sequences is the most effective way to identify (segment) certain subcortical regions. Volume analysis generally falls into two classes: surface-based morphometry (SBM), which measures cortical thickness, and voxel-based morphometry (VBM), which evaluates the relative volumes of grey and white matter in particular brain regions [42]. ALS patients' MRIs evaluate diffusivity, brain structure volumes, and tissue appearance, among other things. People with ALS cannot be identified by routine MRI; ALS patients may have increased corticospinal tract (CST) and corpus callosum intensity [43].

9. Management/ Treatment

9.1. Pharmacological management

9.1.1. Riluzole

Riluzole was permitted for usage in several countries, including the European Union (EU), after the FDA approved it in 1995 for the treatment of ALS in the form of oral tablets. In 2001, the National Institute for Health and Care Excellence (NICE) authorized the medication for use in motor neuron disease in the United Kingdom. As of right now, riluzole is the only medication approved to treat ALS and the only one that has been proven to reduce the disease's progression and increase ALS patients' chances of survival. Since it is a glutamate antagonist, its "antiexcitotoxic" activity is believed to be a key component of its mode of action [44]. Riluzole remains the only drug approved for the treatment of ALS. Different action mechanisms of riluzole are discussed: via its influence on glutamate metabolism, riluzole increases extracellular glutamate uptake and inhibits glutamate release from presynaptic terminals [45].

9.1.2. Edaravone

The US Food and Drug Administration (US FDA) authorized edaravone for use in treating ALS in the US in May 2017. Japan was the first country to use the antioxidant edaravone to treat stroke sufferers. Its exact mechanism of action in ALS is not well understood. Although edaravone did not significantly differ from a placebo in the first phase III research, post-hoc analysis showed that the medicine might be beneficial for a minority of patients in the early stages. As a result, 137 individuals participated in second placebo-controlled multicenter phase III research in Japan that was specifically focused on this subset [46].

9.1.3. Sodium Phenylbutyrate and Taurursodiol Combination (Relyvrio)

Through the reduction of endoplasmic reticulum (ER) stress and mitochondrial malfunction, the combination of these medications has demonstrated an effect in lowering neuronal cell death and oxidative injury. Both medications have been shown to slow the progression of the condition. The histone deacetylase enzyme, which controls transcription and permits regular protein aggregation, is inhibited by sodium phenylbutyrate. Sodium phenylbutyrate was found to enhance cell survival in animal studies. Additionally, this medication raises blood histone acetylation levels, according to clinical investigations. Relyvrio (sodium phenylbutyrate and taurursodiol) was shown to be effective in a 24-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group research [47].

9.2. Emerging modalities

9.2.1. Experimental Stem Cell Therapies

Through the reduction of endoplasmic reticulum (ER) stress and mitochondrial malfunction, the combination of these medications has demonstrated an effect in lowering neuronal cell death and oxidative injury. Both medications have been shown to slow the progression of the condition. The histone deacetylase enzyme, which controls transcription and permits regular protein aggregation, is inhibited by sodium phenylbutyrate. Sodium phenylbutyrate was found to enhance cell survival in animal studies. Additionally, this medication raises blood histone acetylation levels, according to clinical investigations. Relyvrio (sodium phenylbutyrate and taurursodiol) was shown to be effective in a 24-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group research [47]. Because bone marrow mesenchymal stem cells may develop into many lineages and multiply as undifferentiated forms, they are frequently used in a variety of human disorders. Additionally, their safety has been extensively established [48]. A few studies over the last ten years have suggested that using precommitted stem cells to replace dead neurons may help patients regain some of their lost functions and improve their clinical state [49].

9.3. Other therapeutic strategies

9.3.1. Multidisciplinary management

A change in the way that ALS patients get healthcare has led to the emergence of multidisciplinary ALS treatment facilities in recent years. These interdisciplinary ALS clinics, which serve just ALS patients, amass a wealth of resources and clinical knowledge that can help manage and optimize care for this degenerative illness. Despite the paucity of data, some research though not all of it has indicated that ALS patients in multidisciplinary ALS clinics have a higher quality of life and a longer survival time than those in general neurology clinics [6]. Patients with ALS might receive secondary or tertiary services from specialist multidisciplinary (MD) clinics. Numerous medical specialists with ALS expertise work at these facilities. By closely coordinating with the primary care physician and community-based services, these clinics should ideally offer both diagnostic and management services and promote continuity of treatment [50].

9.3.2. Respiratory management [51]

- Examine SNP as an NIV initiation criterion.
- Examine how early NIV introduction affects quality of life and survival.
- Evaluate how NIV compliance is affected by executive dysfunction.
- Analyze how hypoventilation affects executive dysfunction.
- Compare methods for removing blockages in the upper airways at different phases of respiratory and bulbar dysfunction.
- Examine the results of lung testing, NIV compliance, and patients with bulbar dysfunction.

9.3.3. Symptomatic treatments

Both pharmaceutical and non-pharmacological approaches can be used to address additional ALS symptoms. Nuedexta, which is available in the US but not in Europe, may enhance bulbar function. However, the majority of these treatments

for ALS symptoms are focused on managing other illnesses and have not been evaluated in randomized controlled studies.

Spasticity

The majority of ALS patients have spasticity, although very few require treatment. Despite the lack of randomized controlled trials in ALS patients, the most widely used medications are tizanidine and baclofen, both of which are muscle relaxants. An intrathecal pump can be used to deliver baclofen to individuals who have severe, incapacitating spasticity. In addition to being used off-label or as a self-prescribed drug in individuals with ALS, cannabinoids have been licensed for the treatment of spasticity in multiple sclerosis [9].

Cramps

The Cochrane review of trials of different treatments, including one randomized controlled trial of tetrahydrocannabinol, found no evidence to support the use of any specific treatment, despite the fact that cramps are common in ALS. Quinine is the most widely used treatment for cramps, although its use is limited in the US due to reports of uncommon but dangerous cardiac and haematological problems. Levetirecetam has been shown in an open label research to reduce the frequency of cramps in individuals with severe cramps [52].

Pain

Neuropathic pain and discomfort from cramping or spasticity are examples of primary pain in ALS patients. The development of muscle weakness and atrophy, extended immobility that results in degenerative changes in joints and connective tissue, and long-term home mechanical ventilation (HMV), either invasively through tracheostomy or noninvasively through mask interface, are the main causes of secondary pain, which is primarily nociceptive [53].

10. Conclusion

ALS is a complex neurodegenerative disease characterized by progressive motor neuron degeneration, with limited treatment options and a poor prognosis. Despite advances in understanding its genetic and molecular mechanisms, the exact cause remains unknown in most cases. Current treatments, such as riluzole and edaravone, can slow disease progression to some extent, but emerging therapies like stem cell treatments and multidisciplinary management offer promise for improving patient outcomes. Further research is needed to develop effective treatments and address the heterogeneity of ALS phenotypes. Ultimately, a comprehensive understanding of ALS pathophysiology and collaborative efforts are essential for improving patient care and quality of life.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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