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Amyotrophic Lateral Sclerosis: The Disease of the Peripheral Nervous System

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Abstract

A literary review of Amyotrophic Lateral Sclerosis summarizing the most up to date information about ALS. The most recent prevalence and incidence reports globally and specifically the USA are reported. Characteristics of the phenotypes are described and a break down of symptoms and effective diagnosis measures are reported and explained. Genetic and environmental factors are summarized and broken down in layman's terms. Current research and treatments being performed for ALS patients and their future impacts are described.

Keywords

ALS, neuromuscular disease, Lou Gehrig's, muscle wasting, literary review

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Introduction to ALS

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease that causes motor neurons of the spinal cord and brain to slowly deteriorate, resulting in paralysis and, in most cases, death by respiratory failure. In Greek, “amyotrophic” means “no muscle nourishment” which results in muscle wasting away and dying. “Lateral” refers to the location of the motor neurons in the spinal cord that are affected by the degeneration. “Sclerosis” means scarring and hardening and refers to what happens to the regions of neurons as they degenerate (ALS association, 2021). ALS was first discovered by the father of neurology, Dr. Jean-Martin Charcot, when he found a correlation of symptoms between cases occurring from 1865 to 1869. Other neurologists at the time had described symptoms of what would become known as ALS, but Charcot was the first to give the disease a name and definition. To this day, many areas of the world still recognize it as Charcot’s disease (Hulisz, 2018). ALS is also commonly known as Lou Gehrig’s Disease because it ended the life and career of the famous baseball player, Lou Gehrig, in 1939. The disease became internationally known and picked up recognition after his death (ALS association, 2021).

ALS was believed to be fully caused by environmental factors when first discovered and thought to have no genetic links, but advancements in science and technology soon disproved this initial theory, beginning to show the disease was much more complex molecularly than previously understood (Turner and Swash, 2015). Studying ALS and dedicating research to understanding its complex molecular mechanisms and causes is important because these mechanisms and causes are still not fully understood and there is still much to learn about the disease. While there are treatments to slow the progression of ALS and improve the quality of life of patients, there is currently no cure for this terminal illness. While the disease is not

physically painful, it is an excruciating demise for one to lose complete control of their body and independence as they remain as cognitively sharp as they day before the disease began taking its toll. The mental pain an individual goes through as they slowly die from this disease is yet another reason for the importance of understanding and defeating this terrifying disease. This paper summarizes the most up to date research about epidemiology, etiology, progression, current treatments, and future treatments of ALS.

ALS in Society

Prevalence and Incidence

Prevalence rates of ALS increase with age. An American prevalence study from 2016 found that the age group of 18-39 had the lowest rate (0.2 per 1000,000 persons) and the age group of 70-79 had the highest rate (17.2 per 100,000 persons) (Mehta et al., 2016). The estimated prevalence of ALS in the United States is 5.2 per 100,000 individuals with approximately 16,000-20,000 individuals being identified with ALS in 2016, and 6000 new people diagnosed each year (Hulisz, 2018). The average global age of diagnosis of ALS is 62 years old. White males over the age of 60 have the highest prevalence rates for ALS in the United States, while males in general have a higher prevalence rate than females at 7.3 vs. 3.6 (Mehta et al., 2016).

Recent incidence reports of ALS globally found a rate between 0.6-3.8 per 100,000 individuals. In Europe, the incidence report was higher ranging from 2.1-3.8 per 100,000 individuals based on studies in Stockholm, Scotland, Norway, and Italy. Studies from South Korea and China found lower incidence rates of 0.8-1.2 per 100,000 individuals. The difference of incidence rates outside of European descendants suggests a significant difference in Asian and non-Asian populations prevalence rates, which is speculated to be caused by a lower prevalence

of genes known to cause ALS in Asian populations. (Longinetti and Fang, 2019). Prevalence rate of ALS in America is 1.5 times greater for whites than blacks (Mehta et al., 2016).

Survival Statistics

Survival of ALS is variable based on the form of ALS and a patient's prior health status. The mortality rate for patients diagnosed with ALS is 2 to 5 years after symptom onset. Approximately 20% of ALS patients who have a slow form of the disease survive for 5 years, 10% for 10 years and 5% for 20 years or longer. Diagnosis at an older age and the bulbar-onset phenotype are associated with a lower survival risk. Those diagnosed at a younger age and earlier on in symptom onset have a longer survival time. Those with the phenotypes of limb-onset ALS also have a longer survival time associated with them after diagnosis (Hulisz, 2018).). Survival rates vary based upon age, type of onset, and treatments received.

Types

There are 2 primary classifications of ALS: Sporadic (also known as idiopathic) ALS and Familial ALS. Familial ALS occurs due to a dominant gene that triggers ALS and occurs in around 5-10% of all patients with ALS (Hulisz, 2018). For those with familial ALS, symptom onset and diagnoses occur on average 10 years earlier than those with sporadic ALS (Mehta et al., 2019). In extreme cases those with familial ALS can have symptom onset and diagnosis in their late teens or early adulthood and progresses quickly (Hulisz, 2018). Familial ALS diagnosis rates are low because of the strict criteria the patient must meet to be considered familial. In order to qualify for a Familial ALS diagnosis the family must be of sufficient size for more than one person to be affected, there must be a record of previous ALS diagnosis in the family, the ALS phenotype must be consistent enough to be diagnosed reliably, ALS must not be associated with stigma so that it has not been hidden from other family members, the patient must be in

contact with their family, and the patient must have reached the age of risk for ALS (Al-Chalabi & Lewis, 2011). This criterion, along with the overlap of genetic markers between familial and sporadic ALS, make it difficult to classify a case as familial. All other patients (90-95%) are considered to have sporadic ALS. Sporadic ALS primarily affects males at a rate of 67%. The time of onset and diagnoses of those with sporadic ALS is usually in the mid-to-late fifties and early sixties. There is no known exact cause of sporadic ALS, but many environmental risk factors and gene mutations have been correlated with diagnoses of ALS. **(**Hulisz, 2018**)**.

Clinical phenotypes of ALS are diagnosed based on body region of involvement, level of involvement of lower motor neurons (LMN) and upper neurons (UMN), and involvement of non-motor regions. Distinguishing the specific initial phenotypic onset can help doctors predict how quickly the disease might progress, what likely pattern further onset will occur in, and allow for the creation of preemptive treatment plans that will mitigate the effects of the disease as it progresses.

The phenotypes of Spinal Form, Flail Arm, Flail Leg, Bulbar Form and Respiratory Form are diagnosed by the body region of involvement. Spinal form is the major type of ALS and is also known as Charcot's type. Symptom onset associated with this type is asymmetric weakness in a limb around the age of sixty. Within a year, weakness worsens and spreads to another limb, the spinal area and/or bulbar area. Muscle atrophy is common within fascicles along with hyperreflexia of the limbs (Couratier et al., 2020). Median survival time after symptom onset is three years. Flail arm syndrome is another common form of ALS. Patients present symptoms of proximal, progressive, and symmetrical wasting and weakening of the lower motor neurons of the upper limbs. Lower limbs and bulbar muscles tend to be unaffected by this form. It is more frequent in men than women and the survival prognosis is around 8 years with slow progression.

Flail leg syndrome is diagnosed by weakness confined to the lumbosacral spinal cord region. Wasting is symmetrical and distal of the lower motor neurons of lower limbs. Like flail arm, progression is slow and median survival time is 8 years (Al-Chalabi and Orla Hardiman, 2013). Bulbar form is also known as progressive bulbar palsy (PBP). It is characterized by difficulty in speaking (dysarthria) or swallowing (dysphagia) coupled with bulbar muscle atrophy. Bulbar muscles make up the cerebellum, medulla, and pons. PBP compromises approximately 20% of patients with ALS. Survival time prognosis of around 2 years is shorter compared to limb onset phenotypes due to the higher chance of patients developing aspiration and pneumonia because of bulbar muscle atrophy. Respiratory phenotype is the rarest and is characterized by the atrophy of respiratory muscles. In most phenotypes, atrophy of the respiratory muscles is usually last, making the respiratory phenotype the deadliest. Mean survival time is 1.5 years and there have been no patients to survive up to 10 years (Couratier et al., 2020).

Progressive muscular atrophy, primary lateral sclerosis, and hemiplegic forms are diagnosed by the level of involvement of LMN and UMN. Progressive muscular atrophy is a rare form of ALS that is classified as a sporadic type. Onset occurs in adulthood and is due to degeneration of the lower motor neurons, specifically the anterior horn cells and brainstem motor nuclei. It is characterized by progressive flaccid weakness, muscle atrophy, fasciculations, and reduced or absent tendon reflexes. Some patients can later develop upper motor neuron atrophy. Within 19 months of onset of limb weakness, bulbar atrophy usually starts to occur. Median survival time is 4 years (Al-Chalabi and Orla Hardiman, 2013). Primary Lateral Sclerosis is purely upper motor neuron degeneration of the spinal lateral cord and patients typically show sever spastic tretraparesis—weakness in all four extremities. Many patients develop LMN symptoms of degeneration within 4 years of diagnoses and some manifest frontotemporal

dementia. This phenotype encompasses 1-5% of all cases of ALS, is slow progressing, and the mean survival time is around 8 years. Hemiplegic form is the manifestation of unilateral upper motor neuron degeneration. It slowly develops ipsilaterally and eventually spreads to involve the contralateral side. After some time, signs of lower motor neuron degeneration begin to appear. This is an extremely rare phenotype (1% of all patients) and estimated survival times varies based upon individuals but is rarely longer than 10 years (Couratier et al., 2020).

Phenotypes are also characterized based on involvement of non-motor regions. Those diagnosed with ALS can also suffer from frontotemporal dementia, Parkinson's, cerebellar degeneration, vacuolar degeneration of cerebral white matter, autonomic dysfunction, and/or sensory symptoms. However, these characteristics do not define phenotypes in the way that involvement of body region and level of involvement of LMN and UMN do. These characteristics are usually diagnosed in addition to the specific phenotype. Sporadic ALS and familial ALS are almost indistinguishable from each other by phenotype, and therefore other factors in a patient's life must be examined to determine the type (Couratier et al., 2020).

The Etiology of ALS

Symptoms

The initial symptoms of ALS can vary based on the individual. The typical first warning sign that someone may have ALS is the gradual onset of progressive muscle weakness. It is a painless symptom and is often ignored by individuals until more severe symptoms begin emerging. Other common initial symptoms experienced by patients include incoordination manifesting in tripping and dropping things, abnormal fatiguing of the arms or legs, muscle cramps and twitches, slurred speech, and uncontrollable periods of laughter. (ALS association, 2021). Some individuals experience frontal lobe cognitive dysfunction and develop dementia or

Alzheimer's disease. Since initial symptoms are nonspecific and can sometimes mimic symptoms of other neuromuscular diseases, it is difficult to identify the cause of these symptoms as ALS (Longinetti and Fang, 2019).

Symptoms eventually progress into partial loss of limb control and eventually complete loss and total paralysis. Individuals can experience different sequences or patterns of loss of limb control based on the phenotype of ALS they suffer from, or patterns can be completely random. For those with spinal onset, the initial symptoms manifest in weakness of all limbs. For flail arm and flail leg syndrome symptoms manifest in the weakness of an arm or a leg, respectively. For those with bulbar onset, the initial symptom is difficulty in speaking and/or swallowing (Longinetti and Fang, 2019). Weight loss is also a common symptom of ALS due to difficulty with eating and swallowing. In addition, a study done in 2019 by Moglia and colleagues found a correlation in a subgroup of patients between weight loss and ALS due to the body having a higher energy expenditure than normal (Moglia et al., 2019).

The last stage of the disease entails loss of control of respiratory muscles which results in the need for permanent ventilatory support to breathe. Loss of sphincter, bladder and eye muscle control also occurs in late stages of the disease. Since ALS effects solely motor neurons, a patient's sense of sight, touch, hearing, taste, and sound are not affected through the progression of the disease (ALS association, 2021).

Diagnosis

Diagnosing ALS is difficult and does not involve just one test or procedure. Since many initial symptoms are similar to symptoms of other neurodegenerative diseases, making an ALS diagnosis immediately after initial symptom onset is nearly impossible. Many other neurodegenerative diseases are treatable and misdiagnosing a different disease as ALS could

prove detrimental for a patient (ALS association, 2021). Recent studies reported median diagnostic delays of 9 to 24 months after initial symptom onset. A diagnosis usually requires evidence of a progressive spread of symptoms which varies in patients, explaining the delay between onset and diagnosis (Longinetti and Fang, 2019). Diagnosis is performed through a clinical examination and a series of diagnostic tests including a neurological examination, electrodiagnostic tests, blood and urine studies, spinal tap, x-rays and MRIs, muscle biopsies, and nerve biopsies (ALS association, 2021).

The first test performed is a clinical neurological examination to evaluate the response of muscles to command. Patients are first asked about the symptoms they are experiencing, when they began, and how they have progressed. A physical examination is performed and can reveal if there is atrophy and hyperreflexia present in the limbs experiencing symptoms.

The most common electrodiagnostic tests performed are nerve conduction studies (NCSs), sensory nerve action potentials (SNAPs), and needle electromyography (needle EMG). NCSs measure the speed and strength of signals traveling between two points of electrodes placed on the body. NCSs should appear normal or slightly abnormal, but most importantly should show no presence of motor conduction block. A motor conduction block is usually associated with autoantibodies and can be treated with intravenous immune globulin, which is not a characteristic of ALS (Brown and Al-Chalabi, 2017). SNAPs tests should also be normal, and a significant abnormality would indicate a different cause of symptoms **(**Hulisz, 2018). Needle EMGs work by inserting a needle electrode into a muscle and producing fibrillation potential graphs from the electrical activity of the muscle when stimulated. Fibrillation potential is considered equivalent to fasciculation potential and therefore produces information about the activity of the fascicles in the muscle. Graphs that produce positive sharp waves and instability

indicate there is denervation occurring in the muscle (Carvalho et al., 2008). EMGs can also be used to determine if a muscle has been reinnervated based on high-amplitude compound muscle action potentials (Brown and Al-Chalabi, 2017).

Blood and urine samples are tested for complete blood count, electrolytes, liver and thyroid function, creatine kinase, erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, vitamin B, 12 anti-GM1 ganglioside antibody, serum protein electrophoresis, and 24-hour urine protein electrophoresis symptoms **(**Hulisz, 2018). These tests help rule out other disorders in the diagnosis such as peripheral neuropathy, vitamin B_{12} deficiency, Lyme disease, thyroid disease, and metal toxicity. These disorders can all present similar physical symptoms of ALS (Brown and Al-Chalabi, 2017). A recent study in 2019 conducted by Federico Verde and colleagues found that measuring neurofilament light chain (NFL) serum levels was a reliable diagnostic and prognostic biomarker. Researchers measured the NFL serum levels in patients with ALS as well as patients diagnosed with Frontotemporal Dementia, Alzheimer's disease, Parkinson's disease, and Creutzfeldt-Jakob disease. Results found among patients with ALS, serum NFL levels were significantly higher than all other neurodegenerative diseases. Serum NFL levels correlated positively with disease progression rate and higher levels were associated with shorter survival making it a useful diagnostic tool for determining if someone has ALS and at which point in the progression of the disease they are at time of diagnosis (Verde et al., 2019).

MRIs are used to image patients head, neck, and limbs. Imaging of the patient's head and neck reveal if there are any structural lesions affecting motor tracts. Imaging of the limbs gives a visual of the atrophy of the muscles and how it has progressed (Brown and Al-Chalabi, 2017). Spinal taps are not as commonly used in diagnostic testing but are performed to rule out the

possibility of cancer or an infection being present in the cerebral spinal fluid. Muscle and nerve biopsies are typically taken in patients who are suspected to possibly have myopathy. Due to the difficulty of making a diagnosis of ALS, the ALS association recommends patients receive a second opinion after initial diagnosis of ALS (ALS association, 2021).

Genetic and Molecular Factors

ALS causes motor neuron death which eventually leads to the atrophy and death of the muscle fibers they innervate. There are more than 120 genetic variants associated with risk for ALS, but the mechanisms of how many of these variants cause issues is still not well understood. It is believed that motor neurons die due to mutations in genes that involve protein homeostasis and trafficking, axon cytoskeletal dynamics, and disruption of RNA metabolism, stability, and function (Brown and Al-Chalabi, 2017).

Many ALS genes are known to cause ubiquitinated aggregates to form in cells, causing a multitude of problems in the neuron's functioning. The normal function of ubiquitin is to covalently bind to proteins, so they are marked for degradation in the ubiquitin/ATP-dependent pathway. ATP-dependent proteinases rapidly degrade the proteins tagged by ubiquitin and keep the cell healthy. However, in individuals with ALS instead of ubiquitinated proteins being broken down, an accumulation of these proteins is seen. It is speculated that the structural changes of the proteins produced by the mutated genes cannot be degraded by the proteinases. These aggregates lead to deterioration of the cell and loss of cellular function (Rodrigues et al., 1998).

The most common mutated gene in ALS is C9orf72 and is caused by a 6-nucleotide repeat **(**Hulisz, 2018). C9orf72 protein has a role in nuclear and endosomal membrane trafficking and autophagy. It is thought to be neurotoxic for a few reasons. The RNA transcribed from the

repeat ends up in the cytoplasm of the cell where it translates into toxic dipeptides. These dipeptides drive neurodegeneration by forming prion-like polymeric protein aggregates that attack the cell (Turner and Swash, 2015). Studies have also shown mutated C9orf72 to inhibit transportation across the nuclear membrane and cause astrocytic degeneration. It is theorized that the reduction of normal C9orf72 protein levels may also contributes to neurotoxicity (Brown and Al-Chalabi, 2017) (Turner and Swash, 2015).

The most well-known and first discovered gene linked to ALS is SOD1 which encodes for copper zinc superoxide dismutase. There are over 114 known mutations of SOD1 that result in ALS. The function of the dismutase is to convert superoxide into hydrogen peroxide or water which is less harmful to the cell (Brown and Al-Chalabi, 2017). The hypothesis of why mutated SOD1 causes motor neuron loss is because of its toxicity and the aggregations that occur. SOD1 mutations produce proteins that are misfolded and cannot be properly degraded by proteasomes and therefore aggregate in the cell. This proteasome malfunction results in motor neuron death (Boillee et al., 2006). SOD1 also causes alterations in axonal structure and inappropriate mis-accumulation of neurofilaments which are the most abundant and important components of large, myelinated axons. Degradation of myelin sheaths slows the electrical signals neurons send to the muscle fibers they innervate, and eventually complete axon degradation severs the connection to the fibers leaving them to atrophy and die (Boillee et al., 2006).

Two genes involved in RNA homeostasis and trafficking are TARDBP and FUS-TLS. TARDBP encodes for the protein TDP-43, which is a DNA- and RNA-binding protein responsible for the regulation of transport, transcription, stability, and mRNA splicing. The mutation causes it to relocate from the nucleus to the cytoplasm, where it accumulates and causes cellular dysfunction. FUS-TLS encodes for a nucleoprotein that is responsible for the regulation

of gene expression, DNA and RNA binding, and mRNA gene splicing. It has the same mechanisms of pathogenesis as TDP-43 and accumulates in the cytoplasm (Hulisz, 2018). The ALS-related mutation of the proteins heightens the proteins binding capability resulting in self-assembly of proteins and formation of aggregates. This self-aggregation results in motor neuron stress-granules which are toxic to the cell (Brown and Al-Chalabi, 2017).

Three genes involved in cytoskeletal dynamics that experience mutation are DCTN1, PFN1, and TUBA4A. TUBA4A proteins provide integrity that is essential for axonal structure. DCTN1 is involved with axonal transportation of proteins and molecules that nourish the axon and the myelin sheath. PFN1 participates in the conversion of globular to filamentous actin and nerve extension. All these functions are essential in axonal health and when mutations in the proteins result in loss of function it leads to axon degradation and loss of connection with muscle fibers. (Brown and Al-Chalabi, 2017). NEK-1 is the most recently discovered ALS gene variant and has several cellular functions. Some of the NEK-1 functions relevant to ALS are neurite outgrowth, microtubule stability, and microtubule dynamics. Disruption of the microtubule cytoskeleton of axons from mutated proteins explains the axonal degradation seen in ALS. (Kenna et al., 2016). Further research is required on the effects of NEK-1 mutation and the general cellular mechanisms of how ALS mutated genes cause toxicity to motor neurons.

Environmental Factors

Environmental risk factors are difficult to establish as causes due to the nature of most of them being found through correlational studies with no biological evidence to back them up. The most widely accepted environmental risk factor that increases risk of ALS is exposure to lead and other heavy metals. A regional case study of the United States conducted by Andrew and colleagues in 2020 found that individuals who participated in hobbies involving lead exposure

(casting lead bullets, making stained glass with lead joints, using lead sinkers) were associated with a three-fold increase in risk for ALS (Andrew et al., 2020). A population-based study performed in Denmark in 2019 further confirmed these findings. The study found a significantly higher association between individuals having occupations with Pb exposure and rates of ALS (Dickerson et al., 2019). A recent study found that lead can disrupt TDP-43 in cultured neurons, forming nuclear granules and accumulation of insoluble TDP-43. Mutations in TDP-43 have been proven to cause motor neuron death supporting that lead exposure could be a risk factor for ALS (Andrew et al., 2020).

Head trauma is another environmental factor associated with higher rates of ALS. Andrew and colleagues found that the association between head trauma and ALS risk increased for injuries more than 10 years prior to disease onset and was greater with injuries occurring after the age of 30. This agrees with previous studies finding a history of head, neck, or shoulder injuries in ALS patients (Andrew et al., 2020). After a famous soccer played died from ALS, a study of 24,000 soccer players between 1960 and 1996 was conducted and an excess of deaths from ALS was reported. Some believed that playing the sport of soccer increased risk, due to the repeated head-to-ball contact during games that players experience (Al-Chalabi and Orla Hardiman, 2013).

Exposure to organic pollutants and chemicals has also been associated with risk for ALS. A study conducted on plasma concentrations of persistent organic pollutants (POPs) and survival of ALS found that individuals with higher plasma concentrations of POPs had decreased survival rates compared to individuals with lower plasma concentrations (Goutman et al., 2019). Exposure to the neurotoxic non-protein amino-acid BMAA (a cyanotoxin) also has been associated with increased ALS rates. Elevated rates of ALS in the Guam population were linked

to consumption of animals that consumed cycad seeds which contain BMAA (Al-Chalabi and Orla Hardiman, 2013). This is further supported by a study with individuals in military service who were deployed and suffered significant rates of ALS. A study conducted by Beard and colleagues found that veterans who had been exposed to herbicide, nasopharyngeal radium, personal pesticides, and burning agents had higher odds of ALS (Beard et al., 2016).

Although there are strong associations between risk of ALS and these environmental factors, positive correlation does not equal causation. It is possible that these environmental factors have an epigenetic effect and could cause the mutation of genes that result in ALS. However, further investigation into the biological mechanisms behind how these environmental factors could trigger ALS is required (Al-Chalabi and Orla Hardiman, 2013).

Treatment and Therapeutics for ALS

Currently no treatment or therapy provides significant clinical benefit for an individual suffering from ALS. It is essential to provide timely intervention to manage symptoms. Intervention can vary from physical, to chemical, to emotional intervention depending on the condition of the patient at the time (ALS association, 2021).

The best treatment recommended for individuals is bringing in a multidisciplinary team to improve the patient's quality of life and slow the progression of ALS. Multidisciplinary teams typically consist of neurologists; pulmonologists; respiratory, occupational, physical, and speech therapists; social workers; nutritionists; behavioral health specialists; and pharmacists (ALS association, 2021). Neurologists constantly assess, monitor, and treat patients. They are often involved in on-going clinical trials and research and can keep the patient knowledgeable about new emerging treatments. Pulmonologists and respiratory therapists provide the patient with respiratory support and monitor them as their respiratory function begins to decline in later

stages (Hulisz, 2018). Patients can receive a tracheostomy, an incision into the airway with a tube inserted, when respiratory function is minimal. It has been shown to have an extended survival time of up to or over 5 years despite age of onset or type (Al-Chalabi and Orla Hardiman, 2013).

Occupational therapists are important in identifying a patient's challenges with activities of daily living (ADLs) and creating a plan to modify their routine or ways to overcome the challenges. Examples of this could include replacing buttons, zippers, and ties on clothes with Velcro to make it easier to get dressed and wrapping the handles of utensils with foam or rubber to makes them larger and easier to grip. Small changes like these can make going about daily life easier and less frustrating as a patient's abilities decline (ALS association, 2021). Physical therapists can work in tandem with occupational therapists to evaluate what level of exercise is appropriate for a patient without causing further muscle damage. Speech therapists can assist with language as speaking becomes more difficult, as well as evaluate the rate of bulbar atrophy based on the patient's capability to chew and swallow food (Hulisz, 2018). When the time comes speech therapists and nurses can help transition to nasogastric feeding (Brown and Al-Chalabi, 2017).

Social workers and therapists prove invaluable in helping navigate the social service system and talking about hard topics with patients and their families, like end-of-life-planning. Nutritionists are instrumental in making sure that a patient maintains adequate caloric intake and nutrition so that they stay in good health. Pharmacists oversee managing medications and making decisions about when certain medications should be stopped, started, or dosage changed (Hulisz, 2018). A commonly prescribed drug, riluzole, provides slight improvement in survival by suppressing excessive motor neuron firing which slows muscular atrophy (Brown and Al-

Chalabi, 2017). Although these measures cannot prevent the eventual death of a patient, they can ensure that a patient and their family are as well-prepared and comfortable as possible throughout the progression of the disease.

Future Directions

Despite the grim outlook on current treatment for ALS, there is cutting edge research and clinical trials taking place evaluating the efficacy of treatments involving growth factor therapies, stem cells and gene therapies. These emerging treatments give hope for future treatments that can reverse the effects of ALS and provide longer survival times. A phase I clinical trial of insulin-like growth factor 1 (IGF-1) through Intracerebroventricular drug infusion has shown to moderately benefit patients without side effects (Boillee et al., 2006). Continued research on using growth factors to restore nutrition to motor neurons will help to produce treatments that combat motor neuron death. A promising gene therapy is the use of antisense oligonucleotides (ASOs) to target the repeat 6-nucleotide repeat mutation in the C9orf72 gene. Results showed that a single injection of ASOs into ALS mice resulted in decreased production of the toxic dipeptide and did not affect levels of mRNAs encoding non-mutated C9orf72 (Jiang et al., 2016). This finding brings hope for finding more ways to combat and reverse the effects of other mutated genes that are involved in ALS. An experiment performed by Glass and colleagues found success in intraspinal transplantation of human-derived neural stems at high doses. This type of treatment can help delay the onset of ALS and improve chances of survival (Glass et al., 2016). These new types of therapies emerging involving counteracting the effects of ALS on motor neurons is exciting news and could potentially provide a cure for ALS in the next few decades as technology and our understanding improves. One day the diagnosis of ALS may no

longer be the delivery of a death sentence, but just another diagnosis that can be treated and cured.

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