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Amyotrophic Lateral Sclerosis

Abstract

The word amyotrophic is derived from Greek, and means “without nourishment to muscles”, lateral means to the sides and sclerosis means hardened (“What is ALS?,” n.d.). First described by Jean-Martin Charcot in the 1800s, Amyotrophic Lateral Sclerosis (ALS) is a progressive degenerative motor neuron disease. Motor neurons are very important cells, and extremely unique since they can be very long with some motor neurons having a length of over a meter (“Disease Mechanisms,” n.d.).

About 5-10% of the cases of ALS are inherited, which is known as familial ALS or fALS, and it is known as autosomal dominant in these patients (“Amyotrophic lateral sclerosis”, 2019; “ALS - amyotrophic lateral sclerosis,” n.d.). In the 1950s, there was an extraordinarily high rate of ALS diagnosis in Guam. There were about fifty cases of ALS in a group of 25,500 people, five of which were classified as familial cases. This was an indication to researchers that there may have been an unknown underlying cause. A few years later the researchers defined it as familial ALS with dominant inheritance (Mathis, Goizet, Soulages, & Vallat, 2018). In the other cases of this disease, known as sporadic ALS (sALS), the cause is unknown (“Amyotrophic lateral sclerosis (ALS)”, 2019).

In the United States it is often referred to as Lou Gehrig’s disease, from the famous New York Yankee baseball player who had this disease in the 1940s. This specific type of motor neuron disease is the most common form of motor neuron disease in adults (“Amyotrophic lateral sclerosis”, 2015). Motor neurons are the neurons that control movements such as walking, talking, breathing, swallowing and others. These nerve cells expand from the brain to the spinal cord and then to muscles throughout the body that control voluntary muscle movement. When the motor neurons die, the brain can no longer initiate and control muscle movement due to lack of contact (“What is ALS?,” n.d.). This disease causes the motor neurons to slowly degenerate and, eventually, become hardened and die. Without neuronal stimulation to the muscles, the muscles begin to atrophy. ALS affects the motor neurons, cerebral cortex, brainstem and spinal cord (“ALS - amyotrophic lateral sclerosis,” n.d.).

Keywords

ALS, Amyotrophic Lateral Sclerosis, Motor Neuron Disease

Disciplines

Diagnosis | Diseases | Medicine and Health Sciences | Nervous System Diseases

Comments

Written for HS 311: Neuromuscular Physiology.

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Anastasia Georgetson

Amyotrophic Lateral Sclerosis (ALS)

Dr. Drury

Neuromuscular Physiology

Introduction:

The word amyotrophic is derived from Greek, and means “without nourishment to muscles”, lateral means to the sides and sclerosis means hardened (“What is ALS?,” n.d.). First described by Jean-Martin Charcot in the 1800s, Amyotrophic Lateral Sclerosis (ALS) is a progressive degenerative motor neuron disease. Motor neurons are very important cells, and extremely unique since they can be very long with some motor neurons having a length of over a meter (“Disease Mechanisms,” n.d.).

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the motor neurons die, the brain can no longer initiate and control muscle movement due to lack of contact (“What is ALS?,” n.d.). This disease causes the motor neurons to slowly degenerate and, eventually, become hardened and die. Without neuronal stimulation to the muscles, the muscles begin to atrophy. ALS affects the motor neurons, cerebral cortex, brainstem and spinal cord (“ALS - amyotrophic lateral sclerosis,” n.d.).

Risk Factors:

There are many risk factors for this disease including age, gender, genetics, smoking, environmental toxin exposure, and military service (“Amyotrophic lateral sclerosis (ALS)”, 2019; Kiernan et al., 2011). ALS is most common in someone who is between the ages of 40 and 60. Before the age of 65, males are more likely to develop ALS but this discrepancy between genders disappears after the age of 70. 5-10% of people with ALS have fALS, which leads to their children having a fifty-fifty chance of developing the disease (“Amyotrophic lateral sclerosis (ALS)”, 2019). Gene mutations play a big role in the development of ALS. There is believed to be about one to three new cases of ALS diagnosis per 100,000 people (“Amyotrophic lateral sclerosis (ALS), 2015”).

Some studies suggest that people who have served in the military are at a higher risk of developing ALS, potentially due to their exposure to chemicals, metals, traumatic injuries, viral infections, or intense exertion (“Amyotrophic lateral sclerosis (ALS)”, 2019). In addition, cases of athletes with ALS are being reported at an increased frequency, but it is unknown if exercise is a risk factor for ALS or if it is a marker of other underlying mechanisms (Hardiman et al., 2017; Kiernan et al., 2011).

Symptoms:

Symptoms of ALS include atrophic muscles, muscle twitches or spasms, difficulty breathing, trouble speaking, eating problems due to damage of the muscles that control the ability to swallow. In the beginning phases of the disease, the ocular muscles, as well as the bladder and bowel muscles are not affected but can begin to experience atrophy towards the later stages of the disease (Taylor et al., 2017). It is uncommon for patients to experience autonomic issues with ALS, although some patients have bladder, cardiovascular or gastrointestinal dysfunction (Hardiman et al., 2017). Limb or spinal ALS is characterized by muscle weakness and atrophy, usually beginning in one limb. Bulbar onset is classified when patients first notice a struggle with swallowing or speech issues (“Amyotrophic lateral sclerosis (ALS) Fact Sheet”, 2013; Maragakis & Rothstein, 2007). Difficulties with swallowing can lead to malnourishment, which is highly dangerous as individuals with ALS also tend to burn calories at a higher rate (“Amyotrophic lateral sclerosis (ALS) Fact Sheet”, 2013). Although ALS affects the motor neurons, about half of people who develop ALS also develop cognitive abnormalities, such as frontotemporal dementia (“Amyotrophic lateral sclerosis (ALS)”, 2015; “Amyotrophic lateral sclerosis (ALS)”, 2019).

Physiology:

The big picture aspects of ALS are the muscular atrophy, motor cortex atrophy and discoloration, sclerosis of the pyramidal tracts (corticospinal and corticobulbar tracts), thinning of the hypoglossal nerves and ventral roots of the spinal cord (Hardiman et al., 2017). When the corticospinal tracts, lateral and anterior tracts that transport messages from the brain to the spinal cord, and the corticobulbar tracts, where messages from the brain to the cranial nerves are sent, degenerate, the lateral tracts of the spinal cord become scarred. With continued disease

progression, due to the hardening and demyelination of the axons, the neurons will shrink and lead to muscular atrophy (Taylor, Brown, Robert & Cleveland, 2016).

Neuronal complications arise from deterioration that starts in the presynaptic terminal, such as difficulties releasing neurotransmitters in vesicles, neuromuscular junction, in regards to glutamate, or distal axon when there is retraction or denervation (de Carvalho, Eisen, Krieger & Swash, 2014; Hardiman et al., 2017). Fast twitch motor neurons are more susceptible to atrophy versus the slow twitch motor neurons. The fibers that can manage to avoid denervation also have a greater ability to sprout, leading to patients with ALS having a decrease in the amount of motor neurons that are recruited and on occasion, larger fibers are recruited first instead of smaller fibers. This is a disruption in the Henneman's size principle. The decrease and disruption in recruitment of the motor neurons is also a major reason why there is fatigue. The fibers that fatigue first are the fibers that normally die first in patients with ALS (de Carvalho, Eisen, Krieger & Swash, 2014; Hardiman et al., 2017). In addition, ALS results in the retraction of axons and denervation, resulting in muscle weakness (Hardiman et al., 2017).

ALS results in the loss of motor neurons from the anterior horn of the spinal cord, primary motor cortex, the lower medulla as well as effects translated onto glial cells. The demyelination and degeneration of axons leads to discoloration and shrinkage of the anterior nerve roots in the spinal cord which is one of the only large scale things that can be noticed about ALS. However, the most noticeable changes occur in the genome, the mitochondria or in other cell processes ("ALS - amyotrophic lateral sclerosis," n.d.).

At a microscopic level, spinal motor neurons are lost by about half. The loss of axons and change in color of the motor cortex is usually seen in the corticospinal tracts. The skeletal muscle

shows that by the loss of myelinated large fibers. Denervation and reinnervation occurs in conjunction with fiber type grouping (Hardiman et al., 2017). The combination of denervation and reinnervation results in the enlargement of motor units and the fibers. This leads to the reorganization of the fibers, meaning they get closer together. This is known as fiber type grouping (Rossi, Franco & Estevez, 2013; Agamanolis, 2013).

The causes of sALS are mostly unknown. Gene mutations are a known trigger of ALS, but it is mostly unknown what can prompt the genes to mutate (“Amyotrophic lateral sclerosis (ALS)”, 2015). fALS and sALS both can stem from genetics (Taylor, Brown & Cleveland, 2016). Those who develop ALS and have family members with ALS have inherited the gene, but those who developed ALS from a sporadic cause may have been carrying an ALS-causing genetic mutation that can be passed down to their future offspring (“Amyotrophic lateral sclerosis (ALS)”, 2015).

Around 25-40% of fALS cases are caused by a mutation in a chromosome which is also known to cause frontotemporal lobe dementia, and another 10-20% of fALS cases are caused by a mutation in the instructions that the body has to produce the enzyme copper-zinc superoxide dismutase 1, or SOD1 (“Amyotrophic lateral sclerosis (ALS) Fact Sheet”, 2013). SOD1 is an antioxidant enzyme that is located in the nucleus, cytosol, mitochondria, as well as other places in the cell. SOD1 helps to protect cells from reactive oxygen species but the mutation of the gene can lead to a toxic environment. Patients with ALS who have a mutated SOD1 gene present with an increase in the duration of the disease, earlier onset, and the early symptoms often begin in the lower limbs of the body (Mathis, Goizet, Soulages, & Vallat, 2018).

Glial cells, like oligodendrocytes, are also a factor in ALS. This is due to their role in axon myelination and metabolic aid. In patients with ALS, the oligodendrocytes change their shape and then begin to degrade. This can show that as the myelin sheath begins to break down, the propagation of action potentials begins to slow and the oligodendrocytes cannot support the metabolic demands of the axon leading to dysfunction of the axon (Nonneman, Robberecht & Van Den Bosch, 2014).

Glutamate is an excitatory neurotransmitter that helps to send signals between nerve cells. When there is too much glutamate present, it becomes toxic to the cells. The drug riluzole is a glutamate release inhibitor which is used as a therapeutic intervention for ALS. When there is too much glutamate there is a disruption in calcium homeostasis (Mathis, Goizet, Soulages, & Vallat, 2018). This then leads to the death of the motor neurons. In addition, about 40% of 400 patients with sALS were shown to have increased glutamate levels which also correlated with the severity of the disease (Rossi, Franco & Estevez, 2013).

Mitochondria are a necessity to motor neurons. There is increasing evidence that mitochondrial dysfunction plays a role in ALS. Changes in mitochondria can be detected before an individual begins to experience any physical changes (“Disease mechanisms,” n.d.). Motor neurons rely on ATP produced by the mitochondria to regulate a lot of their internal processes. When there is less ATP the motor neurons cannot use the sodium/potassium pump which then leads to slow depolarizations. Dysfunctional mitochondria in a person with ALS may mean that the mitochondria are struggling to produce ATP and may begin producing more oxidative stressors. This can lead to motor neuron loss (Mathis, Goizet, Soulages, & Vallat, 2018).

Calcium is also required to cause muscle contraction. ALS patients have calcium-related complications which may be due to the disruption of calcium channel function. Fluxes in calcium is used to cause or delay cellular apoptosis (“Disease mechanisms”; Mathis, Goizet, Soulages & Vallat, 2018). Disruption in the ability to regulate calcium may lead to proliferation of cells that should have been signaled to induce apoptosis. Additionally, mitochondria aid in calcium homeostasis. When the mitochondria can no longer regulate calcium there can be an increase intracellularly which can lead to neuron death (Rossi, Franco & Estevez, 2013).

Inflammation can become counterproductive to the body if it is left to go on for a long amount of time. Neuroinflammation is suggested to accompany the death of the motor neurons in patients who have ALS (“Disease mechanisms”). Neuroinflammation may be a potential target for therapy, especially in regard to rate of progression of ALS (Morgan & Orrell, 2016; McGreer & McGreer, 2005). Within the spinal cord and brain stem of patients, neuroinflammation can be seen due to the presence of activated glial cells and T-cells (McGreer & McGreer, 2005).

RNA is becoming an increasingly important topic in the research of ALS, especially in regards to RNA processing in regards to translation and transportation (Morgan & Orrell, 2016). In ALS, there are problems transporting neurotransmitter containing vesicles along the axon and also allowing the vesicles to bind and release the neurotransmitters. Cytoskeleton damage can cause the axon to retract from the muscle fibers, disrupting the ability of the neuron to communicate with the muscle fiber by sending action potentials and depolarizing the membrane of the muscle fiber. Astrocytes that do not reuptake extraneous neurotransmitters can also lead to overactivation of these neurotransmitter receptors at the synapse, therefore leading to neuron death (Hardiman et al., 2017).

Frontotemporal Dementia Association:

Previously, patients were informed that with ALS there were almost no cognitive deficits. However, further research shows that a specific gene mutation corresponds to ALS and frontotemporal lobe dementia (Maragakis & Rothstein, 2007; “Amyotrophic lateral sclerosis (ALS) Fact Sheet”, 2013). Frontotemporal lobe dementia is atrophy of the frontal and temporal lobes of the brain which can be seen by MRI. This association with frontotemporal lobe dementia can result in patient compliance difficulties, especially in regards to treatment decisions and compliance (Kiernan et al., 2011).

Diagnosis:

The diagnosis of ALS comes from noting the upper and lower motor neuron dysfunction and the location of the symptoms in the body, since there is no exact test for patients with suspected ALS. Doctors may watch the disease for up to twelve months in order to determine how it is progressing (Maragakis & Rothstein, 2007; Kiernan et al., 2011). Though, the average time it takes to get a diagnosis for this disease is fourteen months. It is essential to watch how this disease progresses in order to avoid providing the wrong treatment since many neuron diseases may have similar presentations (Kiernan et al., 2011). Sensation and autonomic function are usually not involved in ALS, however if symptoms arise concerning these areas, it is an indication that perhaps it is not ALS (Maragakis & Rothstein, 2007).

Electromyography, nerve conduction studies, or MRI can be used to help determine if the patient has a different motor neuron disease. It can also be used to determine if there is lower motor neuron loss. There is normal nerve conduction during the beginning stages of ALS but as it progresses there is a decrease in the amplitude of the action potential (Kiernan et al., 2011).

The MRI can be used to produce images of the brain and spinal cord which can be useful in detecting other conditions like herniated disks that may be causing the patient problems instead of ALS (“Amyotrophic lateral sclerosis (ALS) Fact Sheet”, 2013).

Biomarkers can be used to help determine the presence, rate of progression, or success of an intervention of ALS. Biomarkers can be molecules from the blood or cerebrospinal fluid, an image of the brain or spinal cord, or a measurement of the ability of a nerve to process electrical signals (“Amyotrophic lateral sclerosis (ALS) Fact Sheet”, 2013).

Life-Sustaining Treatment:

There are a few drugs that can help with ALS, but they do not cure the disease. Drugs such as Riluzole (Rilutek), Nuedexta, Tiglutik and Edaravone (Radicava) have been shown to increase survival rates of patients with ALS (“Amyotrophic lateral sclerosis (ALS)”, 2015). Riluzole can assist in decreasing levels of glutamate (“Amyotrophic lateral sclerosis (ALS) Fact Sheet”, 2013). This drug helps to improve the condition of those who were diagnosed with bulbar onset ALS. In addition, riluzole impacts sodium channels and calcium-activated potassium channels (Morgan & Orrell, 2016). This can increase the patient’s survival by three- to six months (Kiernan et al., 2011). By reducing the amount of glutamate, it decreases the toxicity of the environment, improves glutamates role in calcium homeostasis meaning there is a decrease in extracellular levels, leading to potentially less spasticity of the muscles and less neuron death. Edaravone works by relieving oxidative stress, which has been thought to be a contributor to motor neuron death. Oxidative stress is when there is an imbalance in free radicals and antioxidants (“Amyotrophic lateral sclerosis (ALS)”, 2015).

Physical therapy is also a useful tool that can help improve an individual's independence. Aerobic exercises that are low-impact are beneficial to the patient by increasing strength in muscles that are unaffected by ALS ("Amyotrophic lateral sclerosis (ALS) Fact Sheet", 2013).

Prognosis:

The prognosis of ALS is a survival from three to five years after diagnosis, but a more favorable survival rate depends on age, male gender, and limb rather than bulbar symptom onset ("Amyotrophic lateral sclerosis (ALS)", 2015). In addition, the onset of ALS at an older age, bulbar onset and respiratory muscle dysfunction are all typically indicators of a reduced survival rate. Limb onset and a younger age at diagnosis are all indicators of a longer survival (Kiernan et al., 2011).

The leading cause of death in patients with ALS is respiratory failure, since the motor neurons that control the respiratory system are affected in patients with ALS (Kiernan et al., 2011; Delpont et al., 2017). Doctors can monitor a patient's vital capacity by using spirometry, a test where an individual takes a deep breath and then exhales quickly. Malnutrition is also a key factor in ALS. Hypermetabolism can be an indicator of survival, since those who have a hypermetabolism tend to have a shorter survival rate. Doctors can use gastrostomy tubes to provide artificial nutrition and hydration which is used to combat malnutrition caused by atrophy of muscles used to swallow as well as the hypermetabolism that is commonly found in patients who have ALS (Kiernan et al., 2011).

Care, Pain and Quality of Life:

Less than 30% of Americans create advance care directives, which are used to express the patient's wishes in case they become unable to do so themselves in the future. In regards to

ALS, less than 40% have done this. Creating an advance care directive is essential to understanding the kind of treatment the patient would have preferred, especially in the case of ALS when they may no longer be able to communicate due to the disruption of the nerves and muscles that allow you to speak. Opinions on issues such as resuscitation, life-sustaining ventilation and artificial nutrition and hydration are important to have in order for providers to care for the patient in the way they would have preferred (Levi et al., 2017).

Pain may arrive two years before the person begins to experience motor symptoms. The pain from ALS is primarily caused by muscle spasticity (Delpont et al., 2017). This pain may also be a result of immobility. Later on in the disease process, the patient's ability to move and walk is diminished since ALS leads to paralysis. The pain that is associated with these factors may be treated with nonsteroidal anti-inflammatory drugs (NSAIDs), however opioids may be used if these NSAIDs do not provide relief (Ishida et al., 2018). Opioids are addictive and patients will benefit from further research of this disease. More research can lead to more medications that could potentially treat ALS and decrease opioid use. Unfortunately, pain treatment in ALS is not managed well since the mechanics of ALS are still not totally understood (Delpont et al., 2017).

The quality of life of the patient may be improved with therapies such as occupational therapy, speech and language pathology and physiotherapy. In addition, these therapies may help the patient feel more in control, which was found to be an important factor in patients with ALS (Soofi, Bello-Has, Kho & Letts, 2017). The treatment of pain may also improve a patient's perception of quality of life. The amount of pain that a patient feels may lead to the patient feeling more depressed (Ishida et al., 2018). Additionally, there is an increased risk of assisted

and non-assisted suicide in patients with ALS due to feelings of hopelessness or distress.

Antidepressants or anxiety medications may help relieve some of these feelings (Gould et al., 2015).

Conclusion:

Amyotrophic lateral sclerosis is a degenerative disease that affects the motor neurons of the human body. Over time, there is increasing involvement in the eye muscles and bladder muscles, since these muscles are not typically involved in the beginning stages of the disease. There are a few drugs that can help slow the progression of the disease by a few months, but no drug has yet been created or discovered to cure ALS. However, the identification of the genes that cause ALS can help the future research done to better understand how ALS manifests and how it can potentially be treated in the future (“Amyotrophic lateral sclerosis (ALS)”, 2015).

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I affirm that I have upheld the highest principles of honesty and integrity in my academic work and have not witnessed a violation of the Honor Code.