

Muscular Dystrophy Association Motor Neuron Disease Clinic

At
The University of Utah
Department of Neurology

WHAT IS MOTOR NEURON DISEASE?

For many people, ALS is a disorder that they may not know much about. In this handout we will give you general information about the disorder. In other handouts we will answer questions and discuss specific issues.

What is ALS?

Amyotrophic lateral sclerosis is the most common form of motor neuron disease in adults. ALS is a neurodegenerative disorder in which specific nerve cells degenerate and die. There are two types of motor nerve cells that are involved in ALS (see Figure 1). One cell type is called the "upper motor neuron", and is located in the brain. Upper motor neurons send nerve fibers down the spinal cord. The second cell type, called the "lower motor neuron", lies in the brain stem and spinal cord and sends fibers out to muscles. Upper motor neurons "talk" to lower motor neurons, and lower motor neurons "talk" to muscles. Loss of either type of nerve cells results in weakness, and weakness is the major symptom of ALS.

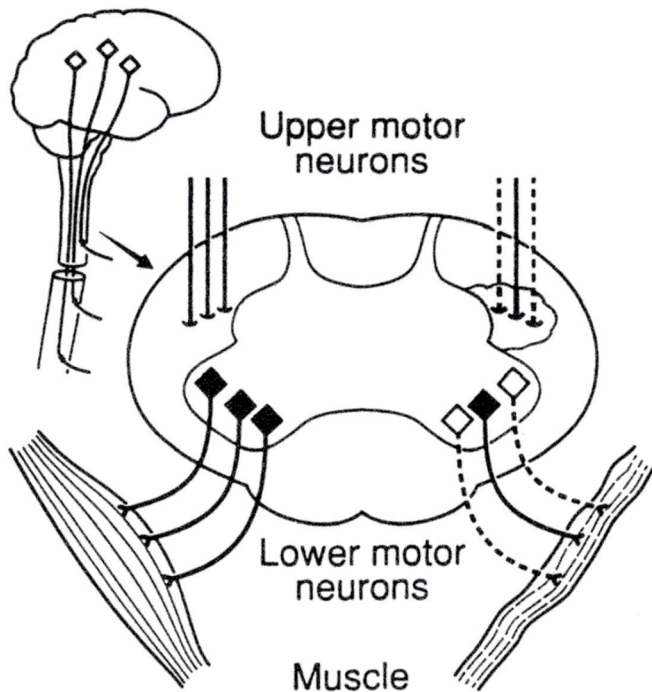


Figure 1: Diagram of the motor system. At the upper left is an outline of the brain and the spinal cord. The position of the upper motor neurons is shown. In the middle is an outline of a slice through the spinal cord. The position of the lateral corticospinal tracts is shown. They contain descending fibers from the upper motor neurons. The position of the lower motor neurons is also shown as diamonds. In the right half of the spinal cord, dashed lines indicate death and degeneration of upper and lower motor neurons, which leads to shrinkage of muscle.

Several names have been used for ALS. ALS is the most common name used in the United States. The more general term "motor neuron disease" is used in the United Kingdom. In addition to ALS, there are other rare forms of motor neuron disease, and we also follow patients with these forms in our clinic. That is why we call the clinic the Motor Neuron Disease Clinic. ALS is also called "Lou Gehrig's disease" in the United States, after the famous New York

Yankee's baseball player who had ALS. However, Mr. Gehrig represents only one individual with ALS, and the course of the disease varies with each person.

ALS was first described in the late 1800's by the French neurologist Jean-Martin Charcot. Dr. Charcot gave the disorder its name, based on what he saw in patients as a consequence of loss of motor neurons (see Figure 1). The term 'amyotrophic' refers to muscle shrinkage when lower motor neurons die. The term 'lateral' refers to the lateral portions of the spinal cord where upper motor neuron fibers travel down the spinal cord. When upper motor neurons die, scar tissue fills in where the nerve fibers used to be in the spinal cord. The scar tissue is firm to the touch, and the term 'sclerosis' means hardening (as in hardening of the arteries in atherosclerosis).

How is ALS Diagnosed?

The diagnosis of motor neuron disease is made from a careful history and a neurological examination. There is no single test available which gives a "yes" or "no" answer, but it is the pattern of findings that allows the neurologist to make the diagnosis. The EMG test is the most helpful test in confirming the diagnosis. Other laboratory tests such as blood tests, and imaging tests such as CT and MRI scans, may help to exclude alternative diagnoses. Sometimes, early in the course of the disease when weakness is mild, it may be difficult to make the diagnosis of ALS. Several visits, perhaps to several physicians, may be required before the diagnosis can be clearly made.

Strictly speaking, ALS involves degeneration and death of both upper and lower motor neurons. While most patients have clear loss of both types of motor neurons, some patients have greater loss of upper motor neurons, while other patients have greater loss of lower motor. These differences do not change the diagnosis. In these circumstances, the more general term 'motor neuron disease' is appropriate.

Important Terms to Know

It is helpful as you read about ALS to be familiar with several medical terms used to describe ALS and motor neuron disease. Nerve cells or neurons are special cells that communicate with each other (see Figure 2). Unlike most cells in the body, nerve cells have a main portion called the cell body, and a long process called the axon. Dendrites project from the cell body, like branches of a tree. Axons are the wires of the nervous system, and can be several inches to several feet long. The upper and lower motor nerves are examples of nerves that are several feet long. Nerves communicate by electrical impulses. Nerves do not touch each other; rather, there are microscopic spaces between nerves called synapses. Impulses transfer from one cell to another at synapses. How messages transfer is a complicated process. At the synapse, a chemical is released from the axon, crosses the space, and interacts with the next neuron's cell body where it produces another impulse. These chemical messengers at the synapse are called neurotransmitters.

In addition to nerve cells, there are support cells surrounding nerve cells. Support cells are of different types and are generally referred to as glia cells. Specific support cells important in ALS are astrocytes. There are about ten support cells for every nerve cell and they are important for nerve cell function and maintenance.

There are many millions of nerve cells in the human nervous system. ALS involves only two nerve cells, the upper and lower motor neurons. The nervous system is divided into regions (see Figure 1). Cell bodies of upper motor neurons are located in the cerebral cortex. The cortex is the biggest part of the brain and is located in the head. Axons of upper motor neurons

travel down the spinal cord to make contact with lower motor neurons. They travel down the sides (lateral portions) of the spinal cord. Cell bodies of lower motor neurons are located in the brain stem spinal cord. Axons from lower motor neurons go out to the muscles; those in the brain stem go to muscles of speaking, chewing and swallowing, while those in the spinal cord go to muscles moving the arms and legs and diaphragm.

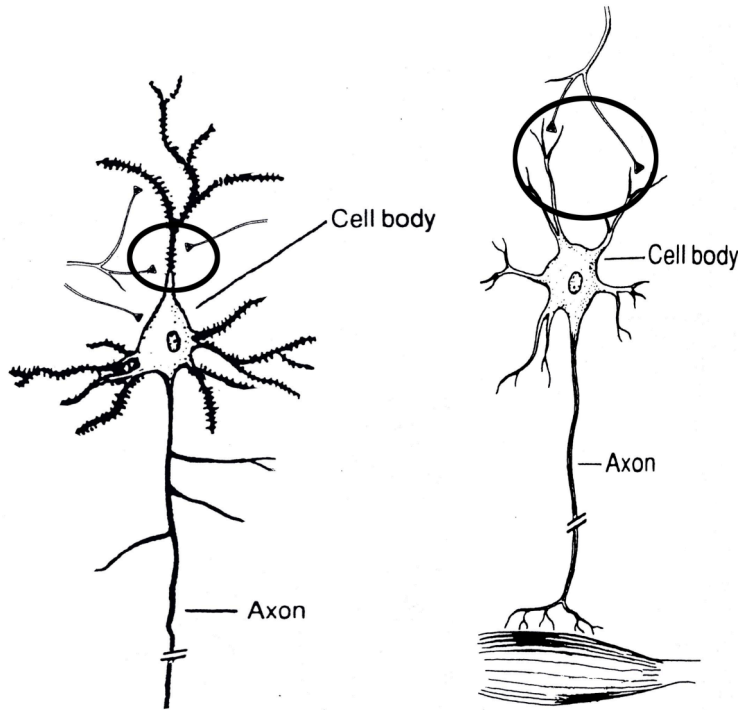


Figure 2: The diagram on the left illustrates the upper motor neuron, and the diagram on the right illustration the lower motor neuron. The important parts are the cell body with its dendrites, and the long axon that interacts with dendrites on other neurons. The dark ovals encircle synaptic connections. In reality, there are many thousands of synaptic connections on each cell body and dendrites. Upper motor neurons make synaptic connections with lower motor neurons.

The region of the brain that controls muscles of speech and swallowing has a special name (see Figure 3), the 'bulb'. The bulb is part of the brain stem that connects the brain with the spinal cord. The name bulb is an old term based on the early observation that this region looks like a tulip bulb. This is why the functions of speaking, chewing and swallowing are frequently called 'bulbar functions'.

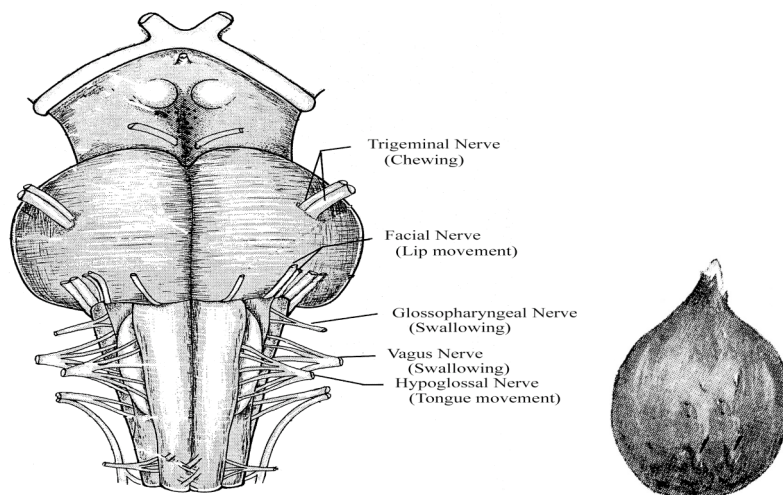


Figure 3: Diagram of the pons or "bulb" portion of the brainstem, showing the nerves (trigeminal, facial, glossopharyngeal, vagus, and hypoglossal) that go to muscle of speaking, chewing and swallowing. This portion was so named because it looked like a tulip bulb.

What Are The Symptoms of ALS?

Symptoms are what a patient feels and describes. Common symptoms are listed in Table 1. It is important to understand that not all patients have all listed symptoms.

Upper Motor Neuron Symptoms: Early speech difficulties are usually caused by loss of upper motor neurons. This is because speech is one of the most demanding muscle movements we make, and any loss of upper motor neurons affects tongue and palatal movements. It may be harder in ALS to make fine hand movements and they may require more mental concentration to perform. Examples are buttoning small buttons. Walking may be stiff. This is termed spasticity. Spasticity can lead to instability when walking. Instability can make it hard to catch one’s balance, and this can lead to falls. Loss of upper motor neurons frequently causes an ease of laughing or crying, and greater difficulty controlling emotions. There may also be more frequent yawning. Another symptom occasionally observed is urinary urgency, where suddenly a patient will have to go to the bathroom.

Table 1: Symptoms of upper and lower motor neuron loss.

UPPER MOTOR NEURON SYMPTOMS	LOWER MOTOR NEURON SYMPTOMS
Difficulties with speech Difficulties with swallowing Slowed and more difficult movements Stiffness of walking Ease of laughing or crying, Increase yawning Urinary urgency	Weakness Shrinkage of muscles Ease of muscle cramps Twitches of muscle Increased fatigue

Lower Motor Neuron Symptoms: The primary symptom of lower motor neuron loss is muscle weakness. Although loss of upper motor neurons also causes weakness, it is not as severe as weakness from lower motor neuron loss. With weakness comes shrinkage of muscles, called atrophy. Muscle cramps may occur in anyone, but are more common in ALS. They may occur at night and cause painful awakenings, or with strong muscle contractions. Twitches of muscle occur in everyone, but occur more frequently in ALS and tend to involve many muscles in the body. Loss of strength frequently results in general fatigue after the usual daily activities.

Who Is Affected by ALS?

ALS is a disease of adults, from age 20 to the very elderly, although the most common age for symptoms to begin is the mid-50’s. Men are affected slightly more often than women. ALS is considered a rare disorder, affecting 2–4 per 100,000 every year. This means that at any given time about 30,000 people have ALS in this country.

Ten to 15 years ago, when the diagnosis was made physicians frequently said that there was no need to be seen again in the office or clinic. Patients tended to disappear from sight. Now, there are more than 50 ALS clinics in the US and many in other countries that follow ALS patients. Patients and family may find that there are many more people with ALS in their community than they realized.

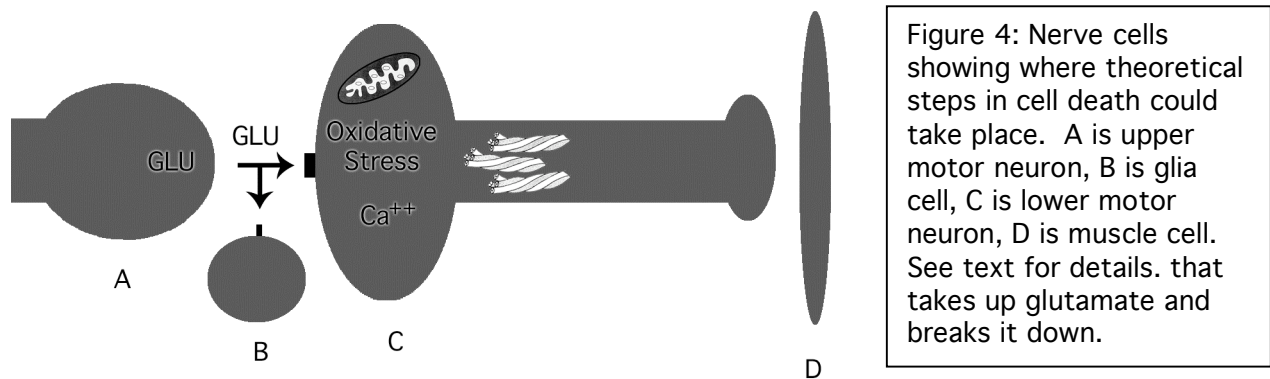
Why Do Neurons Die in ALS?

It is not known why nerve cells die in ALS. There are a number of theories, each with supportive experimental evidence (see Table 2). The theories are frequently linked together, as a cascade of events, which eventually leads to the death of a upper and lower motor neurons. However, at this time our understanding of how these stages are connected is incomplete. Individual

steps serve as a basis of drug trials. Many of these stages are talked about in articles and the internet. The main theories will be reviewed, and Figure 4 illustrates where in the nerve cell these changes might take place.

Table 2: Leading theories of cell death in ALS.

THEORIES OF WHY NEURONS DIE IN ALS
<u>Glutamate Excitotoxicity</u> : excess neurotransmitter can cause cell death.
<u>Increased Cellular Calcium</u> : excess calcium in cells can promote cell death.
<u>Oxidative Stress – Free Radical Damage</u> : damages cells and leads to cell death.
<u>Mitochondrial Damage</u> : energy source for cells, and reduced energy can affect cell function.
<u>Neurofilament Damage</u> : transport system and damage can lead to cell death.
<u>Protein Aggregation</u> : proteins within cells may aggregate (clump) leading to cell death
<u>Single Genes</u> : a small percentage of ALS is likely caused by a mutation in a single gene
<u>Genetic Susceptibility</u> : alterations in genes that are not abnormal may contribute to cell death
<u>Environmental Contributors</u> : may be factor with increased vulnerability.



Glutamate excitotoxicity: Nerve cells talk to each other using neurotransmitters to transfer the signal across the synapse. Glutamate is the neurotransmitter that activates upper and lower motor neurons. Although glutamate is necessary for motor neurons to communicate, too much glutamate may be harmful to nerve cells and cause them to die. Several theories about the cause of ALS focus on why there might be too much glutamate at the synapse. One is that the glia cells are unable to take up and inactivate glutamate as they should. Please note that taking glutamate in the diet, as monosodium glutamate (MSG), does not increase glutamate at synapses.

Increased calcium in cells: Calcium is necessary for many chemical reactions in cells, including nerve cells. However, if too much calcium enters a cell, it could set off events in the cell that lead to cell death. Please note that taking calcium tablets to protect bones does not increase calcium in cells.

Oxidative stress – free radical damage: Oxygen radicals are molecules that are energetically unbalanced; they want to pull off parts from other molecules to restore their energy balance. However, by doing so, they may damage the other molecules. It is possible that these damaged molecules could lead to a breakdown of the nerve cell and death.

Mitochondrial damage: Mitochondria are small particles in all cells that produce the actual energy that cells need. Any breakdown in this process could result in less energy for neurons and set off a range of cellular abnormalities leading to cell death.

Neurofilament damage: Neurofilaments are the transport system of cells. They are very thin strands of protein that help move molecules up and down the long processes (axons) of nerve cells. It is possible that damage to the transport system of nerve cells could hasten their death.

Protein aggregation: Proteins within cells are continuously broken down and new proteins made. There are steps to get rid of old proteins. It is possible that alterations in this process could lead to excel clumps of protein that can contribute to processes that hasten cell death.

Single genes: A small portion of ALS is due to mutations in a single gene. In these situations, the mutated gene produces an abnormal protein that eventually leads to death of upper and lower motor neurons.

Genetic susceptibility: Although we all have the same complement of genes, we also have slight variations in our genes that help make each of us unique. Some of these differences in genes change some of the many chemical reactions that go on in our cells. As yet unidentified genetic differences could lead to susceptibility to developing ALS.

Environmental factors: Environmental factors have always been a question, but none have been identified.

As mentioned above, these represent theories. There is a great deal of research being conducted in laboratories throughout the world to better understand why nerve cells die in ALS. It is hoped that we will gain a better understanding of why cells die and how we can stop their death. Since ALS is a neurodegenerative disease, we can take advantage of research findings from other neurodegenerative diseases such as Alzheimer and Parkinson diseases.

Are There Other Factors That Cause ALS?

It is common to wonder if certain events or happenings at an earlier time in one's life could have contributed to ALS. Events frequently mentioned include past exposure in the environment, trauma, medical conditions, operations, and stress. Studies have been conducted to look for factors, such as ethnic background, where one lived during early childhood and adulthood, type of food (from a grocery store or from a farm), source of drinking water (city or from a well), occupation and hobbies, etc. These studies have identified no clear factors associated with the development of ALS.

A small percentage of patients, about 5%, have other members in the family with ALS. This is called familial ALS. People who have the hereditary form of ALS almost always have a clear family history of the disorder. It is passed down in an autosomal dominant pattern. That means that every child of an affected parent has a 50% chance of receiving the faulty gene. Therefore, if there is no history of ALS in the family, it is highly unlikely that this is the familial form of ALS. Thus, for most patients (95%), ALS just occurs.

How Does ALS Progress?

Motor neuron disease is a progressive disorder that shortens a patient's life. Eventually, the muscles of breathing become weak. Patients with ALS die from respiratory failure. It is not possible to accurately predict when a person will die from ALS. Estimates are guesses at best; patients usually live longer than estimates suggest.

There are a number of ways to measure progression in ALS. First, it is important to understand that nothing happens quickly in ALS. Just as initial problems with strength and function took some time to become real problems, and took some time to diagnose, further progression will be slow.

One way to measure progression is by testing muscle strength. When muscle strength is measured every few months on a special machine, the numbers fall in a linear or steady fashion. When strength is measured by determining how well a person carries out daily activities, there may be periods when some functions may be lost relatively quickly. The apparent difference between steady loss of strength and apparent loss of function can be explained by the 'camel and straw' phenomena. Strength is lost steadily, but when close to the threshold, a small loss of strength results in a big change in function. At the later stages of ALS, the loss of strength tends to slow down.

The diaphragm, the main muscle of breathing, eventually becomes weak. Weakness of the diaphragm also occurs slowly and tends to occur later in the course of ALS. This means that people do not suddenly stop breathing and suffocate, and there is time to discuss breathing issues.

When lower motor neurons degenerate, muscle fibers that were normally activated by the nerve become disconnected and do not contract. This is the cause of muscle weakness in motor neuron disease. Although dying nerve cells cannot grow back, the remaining uninvolved lower motor neurons may send out nerve branches within the muscle to reconnect, or reinnervate, orphaned muscle fibers. This reinnervation of muscle fibers preserves strength. However, as greater numbers of lower motor neurons are lost, the surviving neurons can not keep up and weakness progresses.

What Else Happens in ALS?

Weakness is the major symptom in ALS. Few other issues arise. Vision, hearing and sensation remain normal. Full control of bowel and bladder function is retained, although there may be urinary urgency. Sexual potency also is unaffected but sexual activity may require physical adjustments due to weakness. Pain is not a feature except that there may be muscle cramps that can briefly be uncomfortable. Occasionally there is pain in and about joints that is due to weak muscles (muscle imbalance). These often can be improved by physical therapists.

There is new evidence that about 30% of patients with ALS experience difficulty coming up with the correct words during conversation, difficulty making decisions, as well as some changes in behavior. The changes in thinking are called fronto-temporal dementia. This is clearly different from Alzheimer dementia, where memory function is lost. These changes in ALS are not usually troublesome.

Is There a Cure for ALS?

At this time, we do not have a cure for ALS.

However, there is one medication that can prolong survival. This medication is called riluzole or Rilutek®, and is discussed in detail in another handout.

Is There Research in ALS?

There are many physicians and scientists throughout the world carrying out research on ALS to better understand why it occurs and how to stop neuron degeneration and death. There are a

number of funding agencies, including the US federal government through the National Institutes of Health (NIH), private agencies such as the Muscular Dystrophy Association (MDA) and ALS Association (ALSA), and several private foundations. There are a number of clinical trials of medications conducted in medical centers across the United States and in other countries. We in the Motor Neuron Disease Clinic keep abreast of research on ALS and other forms of motor neuron disease, and are in a position to provide information to you as it becomes available and to answer your questions.

The Challenges of ALS

ALS is a challenging disorder. We are here to assist you. Questions and issues are not the same for every person with ALS. We have a series of handouts that cover specific questions and issues. We hope you will feel free to discuss your questions with us at any time.

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