

# Amyotrophic Lateral Sclerosis (ALS)

There are multiple motor neuron diseases. Each has its own defining features and many characteristics that are shared by all of them:

- Degenerative disease of the nervous system
- Progressive despite treatments and therapies
- Begins quietly after a period of normal nervous system function

ALS is the most common motor neuron disease. One of its defining features is that it is a motor neuron disease that affects both upper and lower motor neurons.

## Anatomical Involvement

ALS is a disease that causes muscle atrophy in the muscles of the extremities, trunk, mouth and face. In some instances mood and memory function are also affected. The disease operates by attacking the motor neurons located in the central nervous system which direct voluntary muscle function. The impulses that control the muscle function originate with the upper motor neurons in the brain and continue along efferent (descending) CNS pathways through the brainstem into the spinal cord.

The disease does not affect the sensory or autonomic system because ALS affects only the motor systems.

ALS is a disease of both upper and lower motor neurons and is diagnosed in part through the use of NCS/EMG which evaluates lower motor neuron function. All motor neurons are upper motor neurons so long as they are encased in the brain or spinal cord. Once the neuron exits the spinal cord, it operates as a lower motor neuron.

## Upper Motor Neurons

The upper motor neurons are derived from corticospinal and corticobulbar fibers that originate in the brain's primary motor cortex. They are responsible for carrying impulses for voluntary motor activity from the cerebral cortex to the lower motor neurons.

Axons from these two tracts (collectively referred to as the pyramidal tracts) begin at the motor cortex of the brain but travel different paths in the central nervous system:

- The corticospinal tract projects to control extremity muscle activity
- The corticobulbar tract projects to cranial nerves

The corticospinal tract fibers traverse through the brainstem where most of them cross at the medulla becoming the lateral pyramidal tract. Their course then continues on down the spinal cord where they travel in the anterior horn before exiting the spinal cord to control extremity muscle activity.

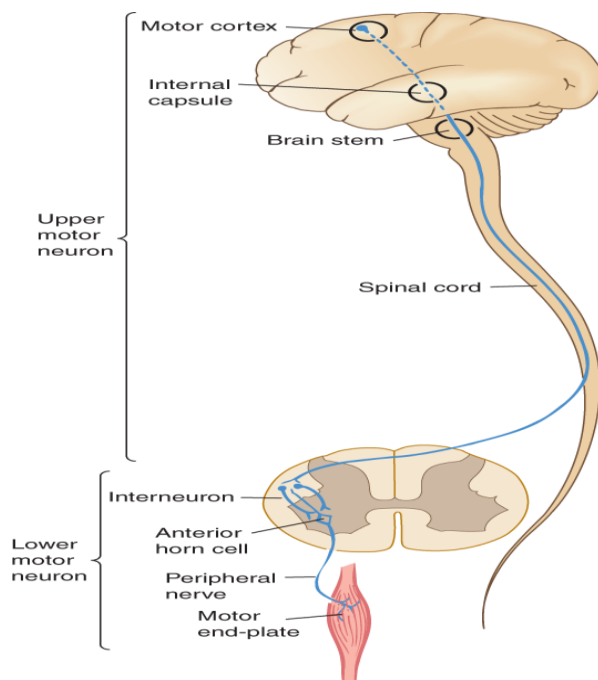
Unlike the corticospinal tract, the corticobulbar fibers do not project down the spinal cord. Instead they provide supply to the cranial nerve nuclei. Most specifically, the corticobulbar fibers affect the following cranial nerves and functions:

- V (Trigeminal – facial, mouth and some tongue sensation)
- VII (Facial – facial expression)
- IX (Glossopharyngeal – salivary controls)
- X (Vagus – laryngeal supply)
- XII (Hypoglossal – tongue innervation)

In some instances, the motor neuron pathways can also affect the brain's limbic system which has impact on mood, expression and memory. This especially occurs in ALS patients who have a more bulbar or corticobulbar involvement with their disease.

### Lower Motor Neurons

Once a nerve exits the spinal cord it is no longer an upper motor neuron, it becomes a lower motor neuron providing direct supply to peripheral structures.



Source: Waxman SG: *Clinical Neuroanatomy: Twenty-Seventh Edition*; www.accessmedicine.com Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

### **Pathway of upper motor neuron to lower motor neuron**

## **History and Incidence**

ALS has been described by physicians for centuries but it is associated with the French neurologist Jean-Martin Charcot who is credited for naming it in 1869. The name Amyotrophic Lateral Sclerosis (ALS) is derived from Greek: *Amyotrophic* meaning 'no muscle nourishment,' *Lateral* refers to the lateral area

in the spinal cord where the corticospinal fibers travel, and *Sclerosis* best describes the scarring that occurs in the spinal cord as the motor neurons deteriorate.

ALS affects men more than women in a 2:1 ratio with approximately 5000 cases being diagnosed yearly.

There are variants of ALS but the most common occurring type is termed 'sporadic' meaning there is no clear link to the cause of disease. The sporadic form remains largely cryptogenic in its etiology.

Speculation and hypothesis have suggested immunologic, infectious, excitotoxic, military service and environmental factors as causes for the disease but nothing has been proven.

Approximately 10% of ALS cases can be diagnosed as genetic in origin. This variant of ALS is referred to as Familial ALS (fALS). It is autosomal dominant in nature and research supports gene mutation as the driving force in this ALS type. If a known gene mutation associated with ALS has been identified, the link to a hereditary etiology is strong. If two or more blood relatives have an ALS diagnosis, its etiology is considered to be familial.

A handful of gene mutations have been identified with ALS with ongoing research to discover others.

One of the most well-known mutations associated with ALS is affecting chromosome 21, referred to as superoxide dismutase (SOD-1).

Another more recent discovery is a mutation to chromosome 9 called C9ORF72 (chromosome 9 open reading frame 72). Research studies found the C9ORF72 abnormality in a large number of patients with familial ALS who also demonstrated frontotemporal dementia as a component of their disease.

## **Clinical Presentation**

The clinical presentation of ALS will vary but most frequently the patient will present with asymmetric weakness and muscle wasting, typically in one limb. Onset in the hand or arm is most common while a lower extremity onset is the second.

A small percentage (approximately 25%) will have a bulbar onset in which the symptoms first present with slurred speech, difficulty with swallowing, drooling (sialorrhea), changes in emotional expression, imbalance or awkward walking. This type of ALS onset correlates well with strong involvement of the corticobulbar fibers that supply the head and neck areas.

As previously indicated, there is a subset of patients who present with dementia as the initial sign of ALS disease. This presentation is believed to be secondary to an inherited gene mutation as there have been studies which have identified a mutation with this type of ALS. The frontotemporal dementia associated with ALS is differentiated from other types of dementia through changes seen on MRI, neuropsychological testing and clinical presentation. This type of dementia affects more behavior, mood, speech and movement than the more common Alzheimer's dementia.

A more unusual form of motor neuron disease is the monomelic form which generally affects younger individuals in their late teens and early twenties. It is most commonly seen in Asia and India and rarely in the United States. This form of amyotrophy does not progress to involve more than one limb.

## **NCS and EMG findings**

ALS patients are nearly always evaluated by NCS/EMG at least once in the neurodiagnostic lab. The study serves as a compliment to the clinical exam in making an ALS diagnosis over another disease process. The NCS is an integral part in the ALS diagnosis as it will disclose any evidence of demyelination or conduction block which would steer the diagnosis away from ALS and toward a motor neuropathy.

The basic NCS study for an ALS evaluation should include

- routine motor studies of the median, ulnar, peroneal and tibial nerves
- sensory studies of the median, ulnar radial and sural nerves
- late response
- bilateral phrenic nerve stimulation if there is respiratory symptoms

The nerve conduction study should be done on the most affected limb(s) and on the contralateral side as indicated by those findings.

Nerve conduction studies in an ALS patient will demonstrate *normal sensory responses* provided there are no superimposed peripheral or focal neuropathies. This occurs due to the dorsal root being responsible for sensory input to the central nervous system and it is unaffected in the ALS pathway where the motor neurons are (in the anterior horn of the spinal cord).

Motor studies *can be* normal in ALS, but will often demonstrate decreased amplitudes especially in the symptomatic limb and/or in more advanced disease. When the axons are affected, distal latencies and conduction velocities remain relatively good unless larger and faster axons are lost.

The late responses can be beneficial in determining if the symptoms are more related to spinal stenosis or radiculopathy versus ALS, but they should not be used as the sole differentiating criteria. Abnormal F-responses are more suggestive of polyradiculopathy than ALS and an abnormality of the H reflex indicates S1 nerve root involvement. Abnormalities in late responses can be seen in the ALS patient especially in the later stages of the disease as motor neurons are lost.

The needle EMG study for an ALS evaluation will check proximal and distal muscles in at least three limbs as well as muscles in the paraspinal and/or craniobulbar areas. A study is considered positive for ALS if neurogenic changes consistent with ALS are found in three of the four body segments

(craniobulbar, cervical, thoracic, lumbar) on needle EMG. Depending on the rate of progression, it may take multiple NCS/EMG evaluations over several months to be able to make a firm diagnosis of ALS.

## **Prognosis and Treatment**

There is currently no cure for ALS. Substantial research has been done and is still ongoing in an effort to determine effective treatments and ultimately a cure.

There are many hypotheses about the etiology of ALS, but the pathogenesis of the disease remains elusive. One of the hypothesis is that the motor neurons become vulnerable by genetic predisposition or by other (presently unknown) environmental factors and are then damaged by the neurotransmitter glutamate.

Another hypothesis is astrocyte cells being detrimental to motor neurons. A recent study found that when human adult astrocytes were placed with embryonic stem-cell-derived motor neurons, the astrocytes triggered a form of regulated necrosis in the motor neuron cells. As a result of this research, there will be more evaluation into the potential of stem-cell involvement in the treatment of ALS.

Presently, patients are offered the drug Riluzole which is thought to prolong survival by a few months. Its method of action is not known but it contains pharmacological properties that inhibit glutamate release, which interferes with transmitter binding at an intracellular level, and inactivates voltage-dependent sodium channels.

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