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## Amyotrophic Lateral Sclerosis, the Primary Motor Neuron Disease

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease that deteriorates upper motor neuron and lower motor neurons of the central nervous system. Jean-Marie Charcot, a French neurologist and physiologist, discovered the disease in his laboratory between 1869-1874. Charcot named and diagnosed the first case of amyotrophic lateral sclerosis after the pathophysiology that he witnessed in his laboratory. He broke down the disease into root words from the Latin language describing his findings, “a” meaning no or none, “myo” meaning muscle, and “trophic” meaning nourishment (Kumar 2011). Amyotrophic therefore refers to no muscle nourishment, when a muscle does not receive the proper nourishment and lacks physical use; the muscle atrophies or wastes away (See Appendix A). The lateral portion of the disease refers to the area of the spinal cord that the descending efferent motor tracts run, and sclerosis means scarring. "Lateral sclerosis" refers to hardening of the anterior and lateral corticospinal tracts as neurons in this tract degenerate and are replaced by gliosis. Charcot compiled his findings and documented ALS as a separate motor neuron disease in 1879 (Kumar 2011). Charcot's influence on the field of medicine opened the way for the study of neurological disorders through correlation of clinical observations and pathological discoveries. He was an insightful figure who lead the way in distinguishing neurological diseases and finding better treatment options for those suffering from these disorders.

The epidemiology of ALS is not entirely understood, as systematic epidemiology has not been thoroughly recorded. Though this information is incomplete, it is understood that ALS occurs throughout the world because of the disease's distinct pathology. The disease does not seem to have any cultural boundaries and is predominately a sporadic disease. ALS is shown to be roughly 90% sporadic and 10% familial worldwide. The majority of individuals with ALS are between the ages of 50-60 years old but familial cases have been shown to affect individuals as young as teenagers also (Bäumer 2014). Being diagnosed with ALS under the age of thirty happens in only 5% of cases in the United States. The literature shows that roughly 30,000 Americans are currently diagnosed with ALS and that males are slightly more affected than women, with a

diagnosis ratio of 1.5 to 1, possibly due to protective hormonal factors in women. Western countries prevalence on average is 5.2 per every 100,000 people (Wijesekera 2009). It is well understood that ALS is not contagious and has no socioeconomic or racial boundaries: presently, the only known risk is having immediate family members who have been diagnosed with ALS.

The major pathogenesis of ALS is the degeneration of Betz cells and other pyramidal cells that are located in the primary motor cortex of the frontal lobe. The degeneration of the corticospinal tracts that begin in the precentral gyrus, pass through the internal capsule, cerebral peduncles, brain stem, and eventually spinal cord whither away. Degeneration of anterior horn cell lower motor neurons, and reactive gliosis are also present as the disease progresses (See Appendix B). Astrocytes, a type of glial cell found in the spinal cord, are vital to the healthy functioning of the central nervous system. Some propose that when these cells fail to reabsorb glutamate, it causes the neurotransmitter to reach toxic levels and leads to scarring in the lateral regions of the spinal cord, also disrupting neural signaling (Leigh 1995). The degeneration of motor neurons and subsequently the lateral corticospinal tracts results in motor weakness with no clear indication of sensory disruption. The Corticospinal Tract has three divisions, the crossed lateral corticospinal tract, the partially uncrossed anterior corticospinal tract, and the fully uncrossed corticospinal tract. Ninety percent of the Corticospinal Tract is fully crossed fibers that travels within the contralateral lateral funiculus and decussate at the pyramidal decussation in the lower medulla. Eight percent of the Corticospinal Tract, or the partially uncrossed Corticospinal Tract travel within the ipsilateral ventral funiculus while the remaining two percent are the fully uncrossed lateral Corticospinal Tract that safeguard against incomplete damage (Sahley 2014). All three divisions are efferent descending fiber pathways that synapse with lower motor neurons in the ventral horn of the spinal cord. The modalities of these tracts are willed and skilled voluntary motor control, especially activation of skeletal muscle of the patient's extremities. While the lateral division innervates distal muscle, the anterior division innervates axial muscle. Damage to these motor tracts can be seen in patients with ALS, especially using fluid-

attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) as seen in Appendix C and Appendix D showing degeneration of these areas. This type of test in which hyperintensity in the posterior limb of the internal capsule is consistent with corticospinal tract degeneration is seen through transverse and horizontal cut images of the brain (da Rocha 2004). The precentral gyrus of the frontal lobe is the primary motor cortex of the brain, also known as Brodmann area four which contains Betz cells. These cells contain long axons that synapse with motor neurons that directly connect to skeletal muscles (Manshadi 2014). When this region experiences pathology, such as in ALS, hyperintensity of the area is shown and neurologists can determine if the corticospinal tracts are intact and healthy or degeneration is occurring.

Since ALS degenerates both upper and lower motor neurons and their respective tracts as noted above, the disease is considered unique to each individual. Lesions to upper motor neurons of this tract will cause spastic paralysis, disuse atrophy, and hyper-reflexia. Lesions to the lower motor neurons will cause flaccid paralysis, significant atrophy, and hypo-reflexia (Manshadi 2014). Before diagnosis of the disease, many patients have difficulty walking due to foot drop, notice weakness in a limb, or experience fasciculations (twitching) of the muscles. As the disease progresses, many patients experience muscle spasticity, muscle atrophy, dyspnea, and dysphagia (Zoccolella 2006). Complications with patients can also arise when the pathology of ALS affects the corticobulbar tracts, which activate muscles served by cranial nerves. Muscles of mastication – particularly the masseter that elevates the mandible, the temporalis that elevates and draws back the mandible, and the medial and lateral pterygoids that protrude and elevate the mandible – can degenerate due to ALS. The mixed mandibular branch of the trigeminal cranial nerve V that originates in the trigeminal motor nucleus innervates these muscles, and if these muscles experience atrophy, patients will lose voluntary movement of them. The tensor tympani and tensor veli palatini in the nasopharynx will tense the velum, which is active during swallowing (Sahley 2014). If the patient does experience muscle atrophy or paralysis in the muscles of mastication, a feeding tube, usually a percutaneous endoscopic gastrostomy tube is used to aid in nutritional eating

and drinking that cannot otherwise be possible under the patient's voluntary control (Czell 2013). Cranial nerves V, VII, IX, X, and XI all contain special somatic-motor components. Trouble speaking arises from innervation of the accessory nerve XI to the sternocleidomastoid muscle that function in opening the mouth used for speaking as well as eating. Cranial nerve VII, the Facial nerve, innervates muscles of facial expression, and cranial nerves IX and X, the Glossopharyngeal and Vagus nerve, innervate muscles of the pharynx and larynx, which play a roll in swallowing and speech (Sahley 2014). Pathology to these respective muscles will cause a patient to take a multidisciplinary course of therapy, medication, and devices to help prolong life and maintain movement of the affected areas.

Diagnosing ALS is a separate complication that physicians experience while trying to aid patients with this disease. Generalized muscle weakness without sensory complications can be seen in a number of disorders such as polymyositis, dermatomyositis, thyroid disorders, electrolyte abnormalities, and autoimmune motor neuropathies (Gordon 2011). ALS is therefore diagnosed by ruling out other disorders. Upper motor neuron damage will result in the Babinski reflex, in which a patient's sole of the foot is stimulated and the toes curl inward and down. This reflex, which should only happen in young children, is a sign of upper motor neuron damage that can be caused by ALS. Physicians will also look for stiffness and spasticity of the muscles of the patient while also checking brisk reflexes using a reflex mallet to rule in upper motor neuron damage. Difficulty of producing sounds and articulating words, respectively dysphonia and dysarthria are also common among patients with bulbar onset ALS patients (Zoccolella 2006). Physicians can rule complications with those cranial nerves when a patient exhibits a loss of gag reflex or masseter reflex of the trigeminal nerve V, which will be quite noticeable. Approximately two thirds of patients with ALS initially present with muscle weakness in the upper or lower limbs and approximately one fourth of patients presents with progressive dysarthria and dysphagia, also known as bulbar-onset ALS.

Since ALS is a rapidly progressive neurological disease, there is no current cure. As the scientific community is in search of a cure for neurodegenerative diseases, it

currently takes a multidisciplinary course of action to prolong life in patients diagnosed with ALS. Glutamate, the mostly excitatory neurotransmitter in the central nervous system, may play a role in ALS. Excess glutamate can be toxic and cause degeneration in the central nervous system. Excitotoxicity can occur when glutamate receptors, such as NMDA or AMPA, are over activated. Once these receptors are open, excess accumulation of intracellular calcium and sodium occurs leading to neuronal death or injury (see Appendix E). The only FDA approved drug to counter this problem and to aid the slowing of ALS is Riluzole, or brand name Rilutek. It is a glutamate-release inhibitor that is shown to prolong patient's survival by up to four months, and lengthen the time needed before ventilation support must be given for survival (Gordon 2011).

Physical and occupational therapists are another source of healthcare provision that can help manage a patient's ALS. Pain is not a direct consequence of ALS but immobility of the body and joint contractures can cause weakness, muscle cramps, and pain. As a result, physical therapists can help through range-of-motion exercises and accessing limb strength. As the disease progresses, muscles will start to weaken and stiffen, physical therapists may also help to loosen the muscles and prevent contractures from occurring. Low impact aerobic exercises may aid patients with fatigue, depression, and improve cardiovascular health. Occupational therapist can develop and address skilled motor functions that help aid patients in daily activities. Occupational therapist can also suggest at home changes such as ramps or walkers that help individuals remain mobile with the least amount of stress on the body. Speech pathologist and respiratory therapists will also be needed to aid in the progression of ALS, especially patients that have bulbar-onset ALS. Eventually all muscles that aid in breathing, specifically when the diaphragm and chest wall fail to function properly, ventilation support must be given for survival (Naganska 2011). Since ALS is a fatal disease, the goal of therapy is to aid and achieve the highest quality of life for patients with ALS. Other non-pharmacological therapies can help manage the numerous symptoms that may arise in ALS patients through communication devices, voice amplifiers, and wheelchairs, as seen with one of the most famous ALS patients in the world, Stephen Hawking.

Since ALS is rapidly progressive in nature, life expectancy is three to five years after being diagnosed, though roughly 10% of ALS patients survive for ten or more years (Gordon 2011). Overall, ALS is considered a troublingly harsh and multifaceted form of neurodegenerative disease. While motor function is progressively being lost, patients can also undergo dementia and cognitive complications. Understanding the anatomy, clinical symptoms, and diagnosis of the disease can help healthcare providers prolong life and try to achieve the greatest quality of life for individuals who are diagnosed with amyotrophic lateral sclerosis.

## Appendix A

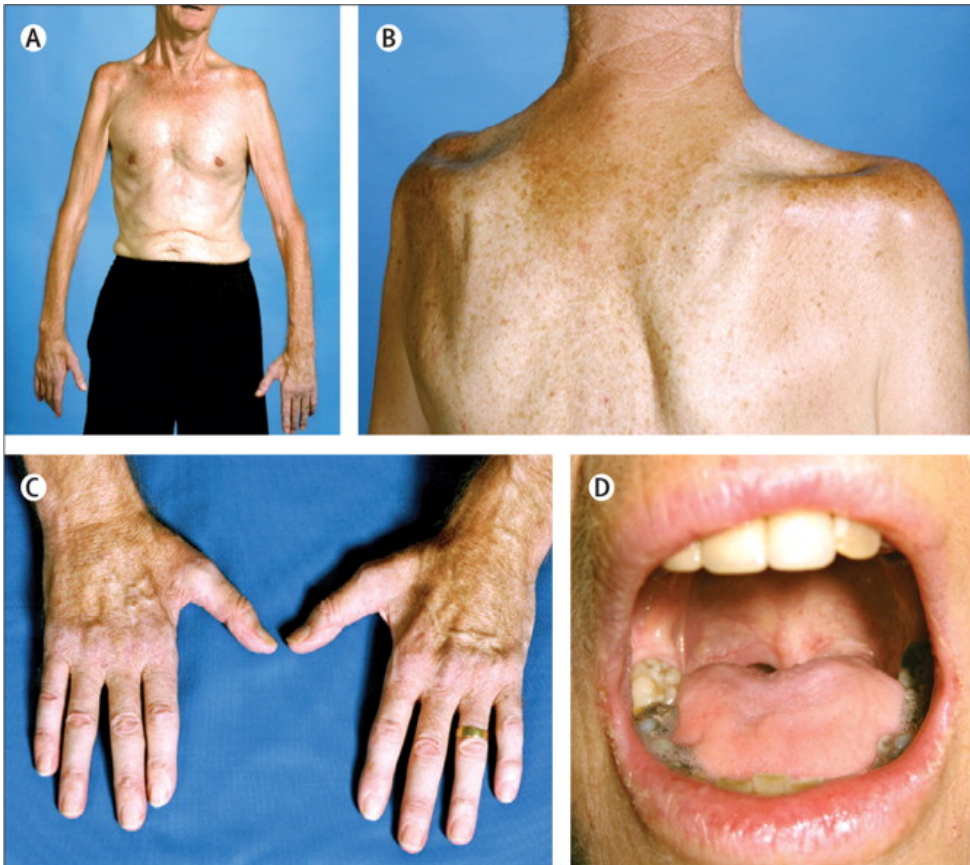
Clinical features of muscle atrophy in a patient with Amyotrophic Lateral Sclerosis

(A): Proximal and symmetrical upper limb wasting which will not allow the patient to lift his arms against gravity

(B): wasting of supraspinatus, infraspinatus, and both deltoid muscles, with recessions superior and inferior to the scapula.

(C): Wasting of the thumb muscles and first dorsal interossei muscle

(D): Wasting of the tongue muscles can make it difficult for patients to elevate the tongue when speaking

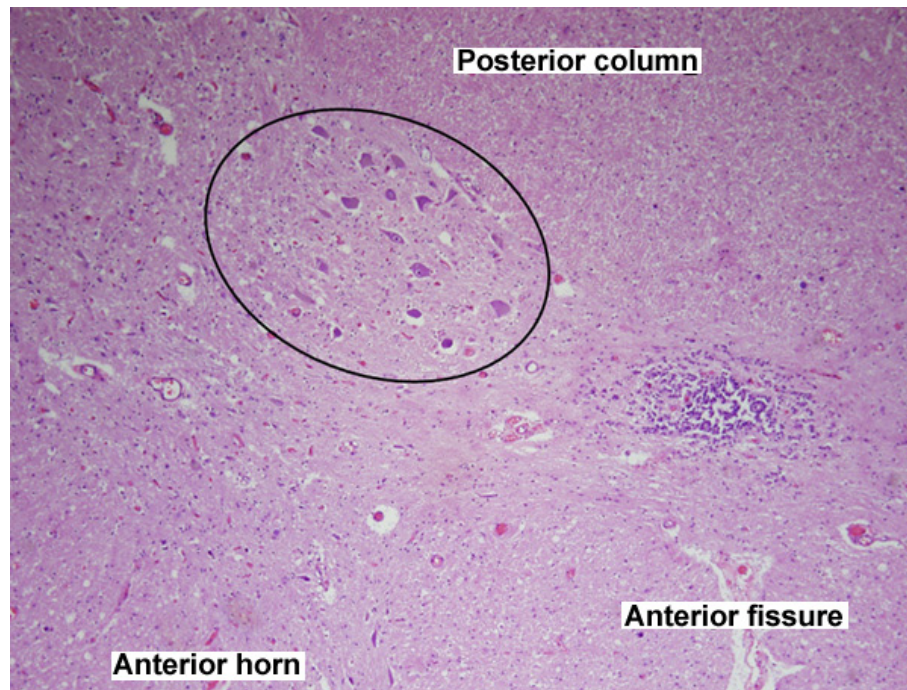


[Muscle atrophy in ALS patient. Digital image. *The Lancet Neurology*. N.p., n.d. We]



## Appendix B

Histologic features of a patient with ALS, this image is of the spinal anterior horn where degeneration, loss of neurons, and severe gliosis is occurring. The circled part of the image is of a healthy Clarke's column, the relay center for unconscious proprioception.



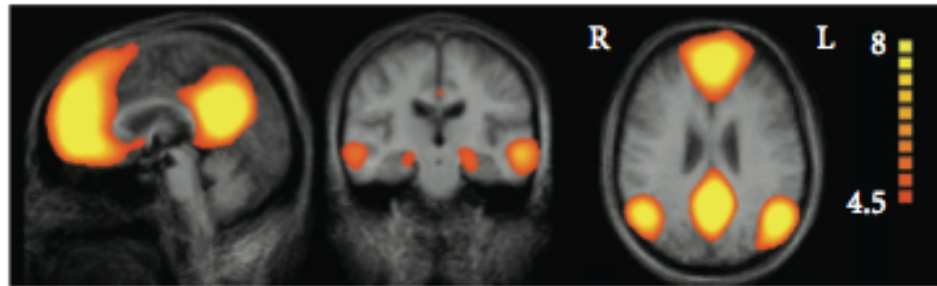
Amyotrophic lateral sclerosis, spinal cord shows gray and thin or atrophic anterior nerve roots.



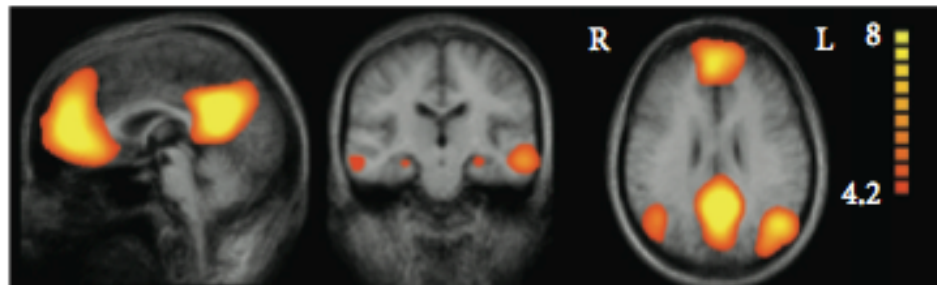
[Takei, H., & Adesina, A. (2014, April 29). Pathology of Motor Neuron Disorders . Retrieved August 7, 2014.

## Appendix C

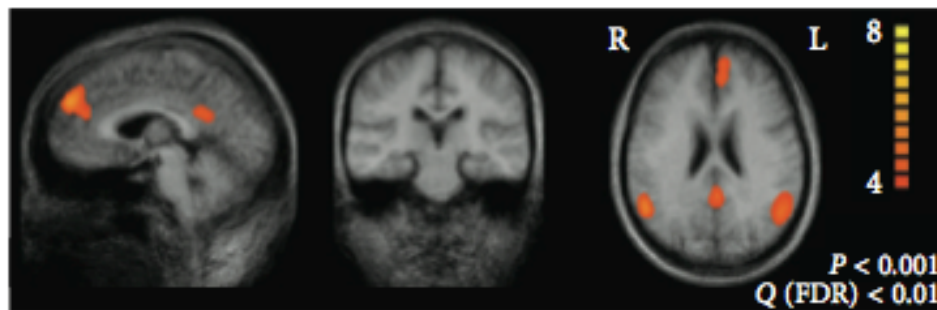
- (A) Shows the result of the control group.
- (B) Shows the results for the ALS patients.
- (C) Shows the statistical comparison is shown between the patients.



(a) Healthy



(b) ALS

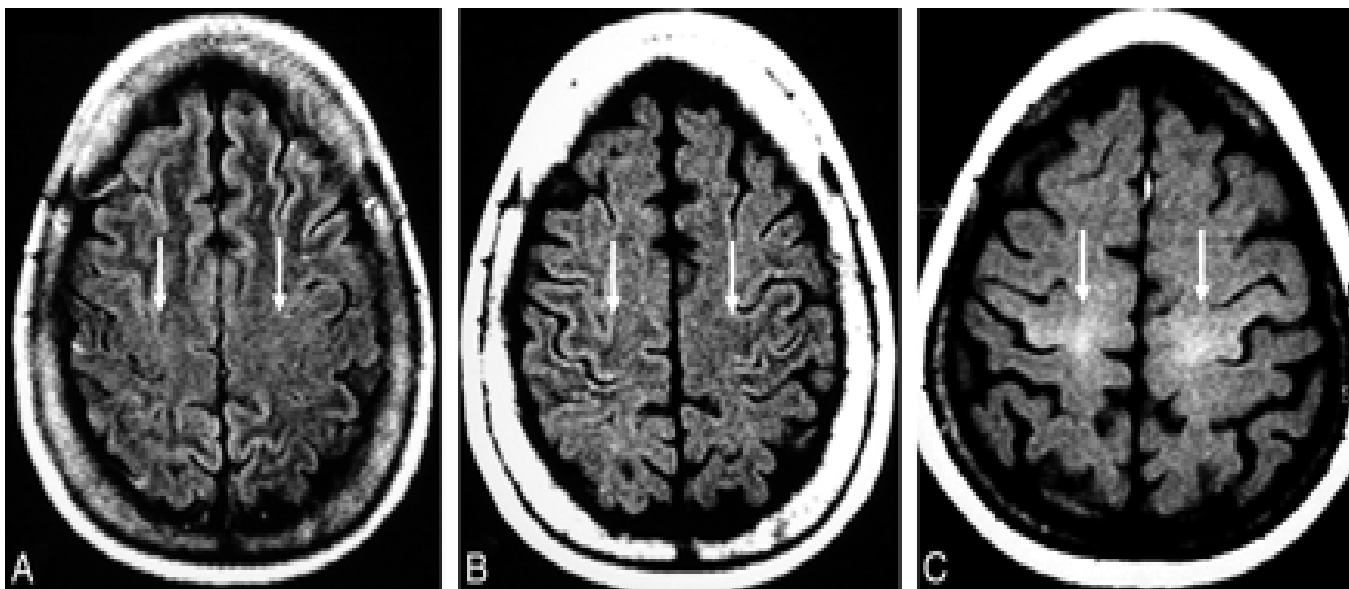


(c) Healthy > ALS

[Kollewe, K., Körner, S., Dengler, R., Petri, S., & Mohammadi, B. (2012). Magnetic Resonance Imaging in Amyotrophic Lateral Sclerosis. *Neurology Research International*, 1-9.]

### Appendix D

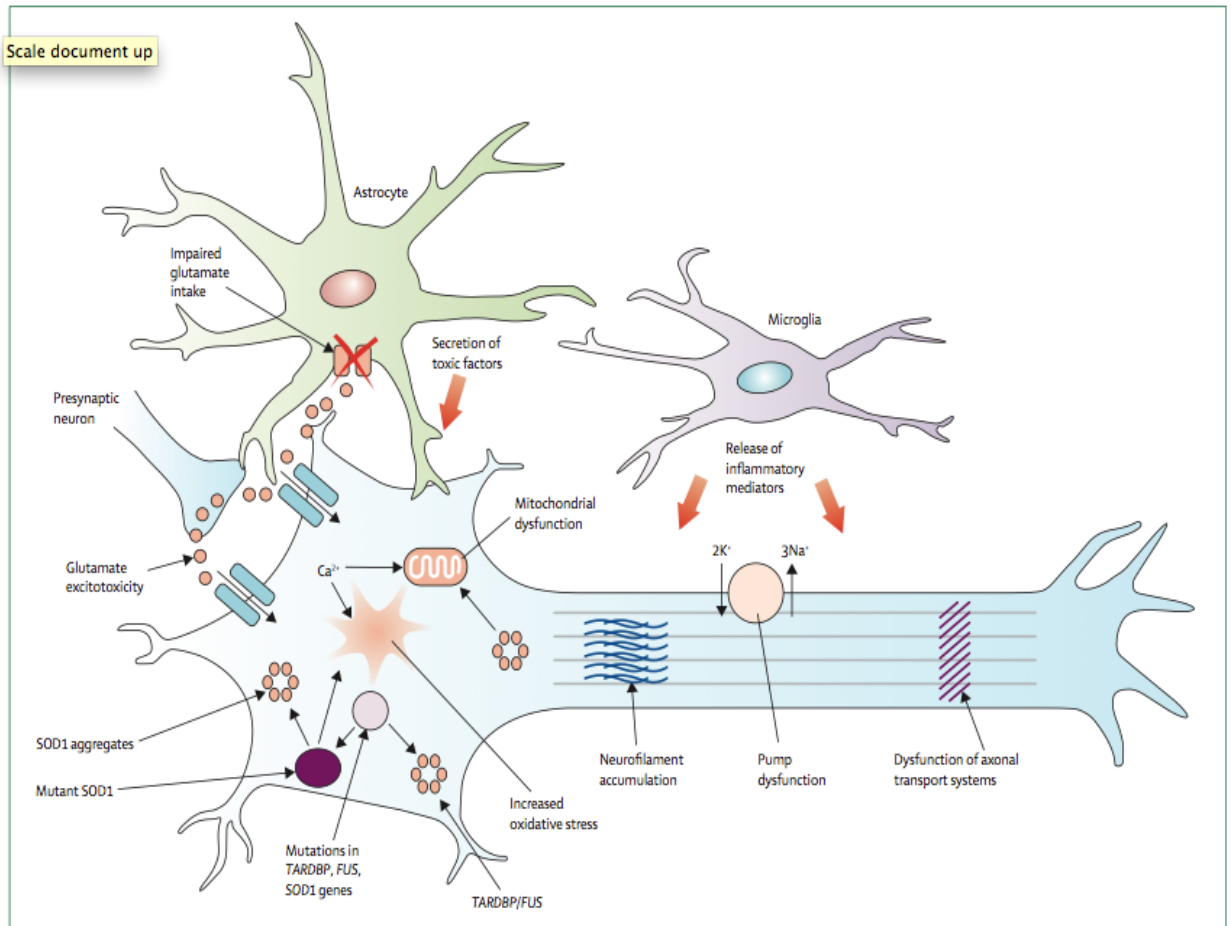
- (A) Image of a control subject showing subcortical precentral gyral isointensity.
- (B) Image of control subject showing subcortical precentral gyral hypointensity.
- (C) Image of ALS patient showing pathologic hyperintensity in the cortical and subcortical regions of the precentral gyri.



[da Rocha, A., Oliveira, A., Fonseca, R., Maia, A., Buainain, R., & Lederman, H. (2004). Detection of corticospinal tract compromise in amyotrophic lateral sclerosis with brain MR imaging: relevance of the T1-weighted spin-echo magnetization transfer contrast sequence. *AJNR. American Journal Of Neuroradiology*, 25(9), 1509-1515.]

## Appendix E

The mechanisms that operate in the neurodegeneration of ALS is not entirely understood but must be multifactorial. Most of the literature note that there is a, “complex interaction of glutamate excitotoxicity, generation of free radicals, cytoplasmic protein aggregates, SOD1 enzymes, combined with mitochondrial dysfunction, and disruption of axonal transport processes through accumulation of neurofilament intracellular aggregates. Mutations in *TARDBP* and *FUS* result in formation of intracellular aggregates, which are harmful to neurons. Activation of microglia results in secretion of proinflammatory cytokines, resulting in further toxicity. Ultimately, motor neuron degeneration occurs through activation of calcium-dependent enzymatic pathways” (Kiernan 2011).



[Matthew C Kiernan, Steve Vucic, Benjamin C Cheah, Martin R Turner, Andrew Eisen, Orla Hardiman, James R Burrell, Margaret C Zoing, Amyotrophic lateral sclerosis, *The Lancet*, Volume 377, Issue 9769, 12–18 March 2011, Pages 942-955, ISSN 0140-6736]

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