Amyotrophic Lateral Sclerosis (ALS): Understanding the Progressive Journey, Unraveling the Mystery of Motor Neuron Disease

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What is ALS? The Core Definition :

- ALS is a progressive neurodegenerative(dysfunction of motor neurons) disease that primarily affects motor neurons.

- **Motor Neurons:** These are specialized nerve cells in the brain and spinal cord that control voluntary muscle movement (e.g., walking, talking, breathing). motor neurons don’t regrow due to this the loss cannot be recovered .

- ALS do not effect the non voluntary muscles like heart beat(cardiac muscle) , digestion etc

- **Non voluntary :** muscles are those which are not controlled my us , they are controlled Autonomic Nervous System (ANS)

- **Impact:** When motor neurons die, signals from the brain cannot reach the muscles. Muscles weaken, waste away (atrophy), and eventually become paralyzed.

- **Key Characteristic:** The mind and senses are typically spared, leaving the individual fully aware of their declining physical abilities.

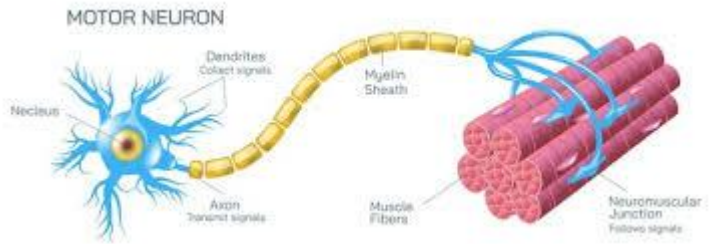
Recognizing ALS: Common Symptoms :

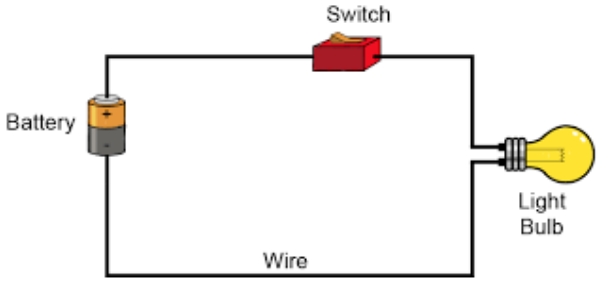
- **Limb Onset:** Weakness or stiffness in a hand, arm, leg, or foot (e.g., difficulty gripping, foot drop).
- **Bulbar Onset:** Slurred speech/difficulty in speaking (dysarthria), difficulty swallowing (dysphagia), or changes in voice.
- **Other Early Signs:** Muscle cramps, fasciculations (muscle twitching visible under the skin), fatigue.
- **Progression:** Weakness spreads from one body region to others as more motor neurons are lost.
- If the patient has ALS all these symptoms gets gradually worse and leads to complete paralysis of body due to end of motor neurons and leads to death of the patient

NOTE: If these symptoms are visible then it can‘t be classified as ALS, many other disease like HIV-aids also cause similar symptoms

From Switch to Muscle: An Electrical Analogy for ALS :

When we switch on a light, the light comes on almost instantly, and vice versa. This quick response is due to the incredibly high speed of electrons, which means the current isn't significantly affected by the wire's resistance over short distances. However, as the length or thickness of the wire increases, its resistance also increases, causing the current to decrease. Due to this, the bulb might not glow (or glow dimly) when switched on or off. This doesn't mean our brain (the source /battery) or our skeletal muscles (the bulb) are damaged. Instead, we would need to increase the electrical potential across the source and the bulb to overcome the increased resistance, perhaps using step-up transformers. Similarly, in ALS, the speed of nerve signals remains consistent, like electric current, but the problem arises from the degeneration/damage and eventual loss of motor neurons. This means the nerve impulses cannot effectively reach the muscle tissues. This progressive weakening and ultimate breakdown of the connection between our brain and skeletal muscles doesn't imply that the brain or the muscles themselves are not functioning; rather, the communication pathway between them becomes increasingly compromised or damaged as time progress .





Types of ALS :

Based on how classical ALS is caused its primarily divided into 2 types

1 **Sporadic ALS :** Sporadic ALS (SALS) refers to cases of Amyotrophic Lateral Sclerosis where there is no known genetic cause or family history of the disease.

About 90-95 % of SALS are of Sporadic ALS

The cause of SALS are still unkown but there are some of feature which are suspected to be key reason for SALS

- genetic variations (polymorphisms)
- Environmental Factors (trauma , infection ,toxic exposure)
- Internal Cellular Mechanisms / Biological Dysfunctions(oxidative stress , Neuroinflammation , Mitochondrial Dysfunction , Protein Misfolding and Aggregation)
- Aging(more found in the age range of 40-70)

2 Familial ALS : Familial ALS is diagnosed when a person has ALS and there is a history of the disease in their family, suggesting a genetic cause passed down through generations.

FALS is caused by genetic mutation inherited by our ancestors

Key Genes Involved**:** Over 40 genes have been identified that can cause FALS. Some of the most commonly identified genes include:

- **C9orf72:** This is currently the most frequent genetic cause of FALS (and also contributes to some sporadic cases), sometimes also linked to frontotemporal dementia (FTD).

- **SOD1 (Superoxide Dismutase 1):** Historically, this was one of the first genes linked to FALS.

- **TARDBP (TDP-43):** Mutations in this gene lead to abnormal TDP-43 protein, a common pathological hallmark found in most ALS cases.

Diagnosis , prevention , treatment of ALS :

Currently there is no treatment to completely cure the disease but we can delay the final stages of this disease
If we diagnose the disease in the earlier stage

Disease-Modifying Medications (Examples):

- Riluzole & Edaravone : Slow disease progression.
- Tofersen (Qalsody) : For specific SOD1-ALS case

Self diagnosis:

There is **NO** accurate "self-test" or online questionnaire that can diagnose ALS. Self test may increase the chance if False-positive(causes unnecessary anxiety) or False-negative (Can lead to dangerous delays in seeking professional)
diagnosis must be done by professional doctor

Advanced stages of ALS :

- **Progressive Paralysis:** As the disease advances, weakness spreads, leading to widespread paralysis.

- **Breathing:** Respiratory muscles weaken, requiring assistive devices like BiPAP or mechanical ventilation.

- **Swallowing:** Difficulty swallowing becomes severe, often requiring feeding tubes for nutrition.

- **Communication:** Speech may become impossible, necessitating assistive communication devices (e.g., eye-gaze technology).

- **PBA(Pseudobulbar affect):** PBA is a consequence of another neurologic disorder or brain injury. Patients may find themselves crying uncontrollably at something that is only slightly sad, being unable to stop themselves for several minutes. Episodes may also be mood-incongruent a patient may laugh uncontrollably when angry or frustrated, for example. Sometimes, the episodes may switch between emotional states, resulting in the patient crying uncontrollably before dissolving into fits of laughter.

Statistical inferences:

Kings ALS staging system and prognosis at each stage

	Stage 1	Stage 2	Stage 3	Stage 4
Stage description	Symptom onset, involvement of the first region	2A: Diagnosis 2B: Involvement of the second region	Involvement of the third region	4A: Need for a feeding tube 4B: Need for non-invasive ventilation
Median time to stage	13.5 months	17.7 months	23.3 months	4A: 17.7 months 4B: 30.3 months

MiToS ALS staging system and prognosis at each stage

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Stage description	No loss of a functional domain	Loss of 1 domain	Loss of 2 domains	Loss of 3 domains	Loss of 4 domains	Death
Probability of death at each stage	7%	26%	33%	33%	86%	

References:

1 videos:

Interview of the patient who are suffering from ALS their life before and after ALS diagnosis , and suffort they got from EverythingALS.org

- https://youtu.be/o8NVY9BFz-E?si=-xNBymrmgxq2qPYD
- https://youtu.be/r5uUHR7dL_Q?si=wG3cNUcJeWw8VNWp
- https://youtu.be/PmbFs90QP8k?si=OtFtVpFzqB5HpLfn

2 articles :

- article on biomarker (machine learning and NLP): https://www.bio-itworld.com/news/2024/03/13/citizen-driven-research-aids-development-of-digital-biomarkers-for-als\
- Impact report and goals of EverythingALS.org up to 2030 for early diagnosis of ALS and its treatment using AI : https://www.everythingals.org/_files/ugd/6f4f2a_49f67417033242b0905d3dbbdf70f6a9.pdf

- Wikipedia ALS cause ,diagnosis ,symptoms , history etc : https://en.wikipedia.org/wiki/ALS#Cause