Amyotrophic Lateral Sclerosis

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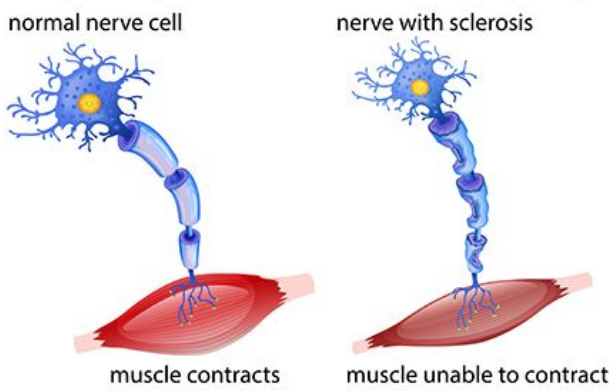
Amyotrophic Lateral Sclerosis

clinical finding of muscle atrophy + hardening of the lateral corticospinal tracts

"a progressive neurodegenerative disease that causes **UMN** and **LMN** symptoms."



UMN

- Frontal lobe motor neurons in the motor strip (Brodmann area 4) and their axons traversing the:
  - Corona radiata
  - Internal capsule
  - Cerebral peduncles
  - Pontine base
  - Medullary pyramids
- Lateral corticospinal tracts of the spinal cord

Autopsy: the dorsolateral area of the spinal cord (lateral corticospinal tract) is gliotic and hardened or sclerotic

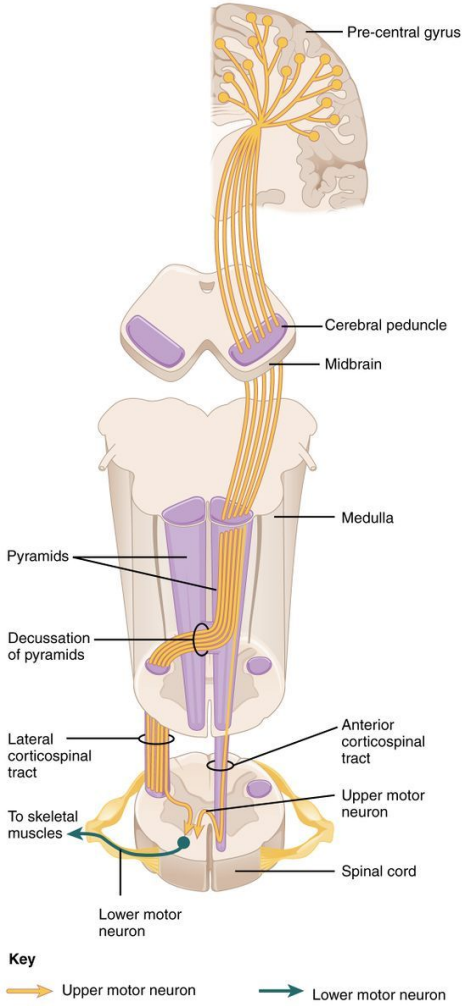
- Hyperreflexia
- Hypertonia
- Spasticity (esp. Lower limb)

LMN

- Brainstem
- Spinal cord

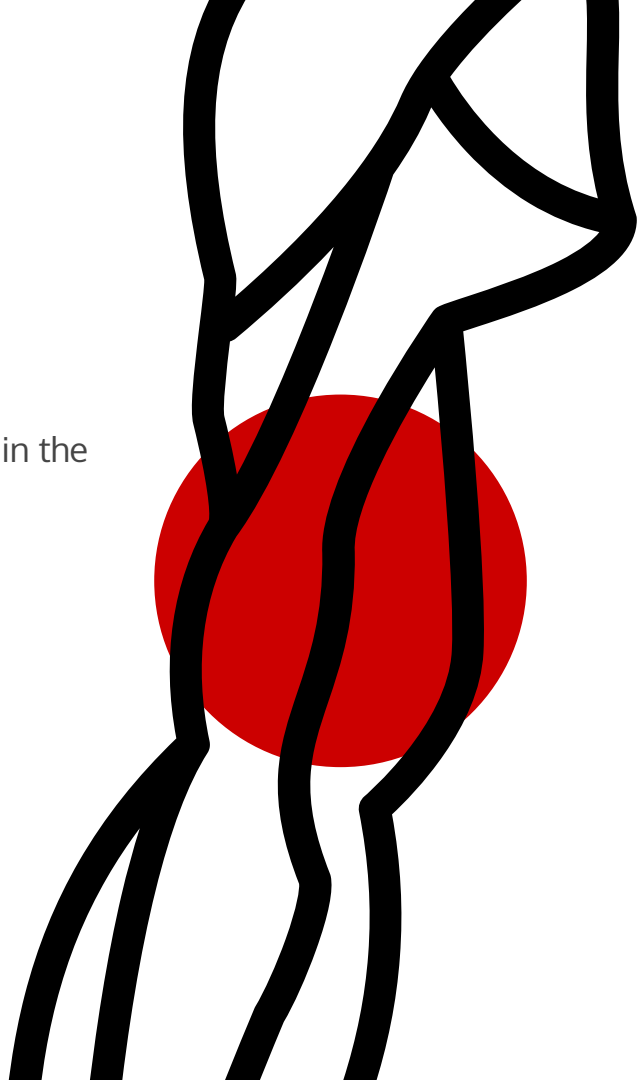
- Atrophy or amyotrophy
- Fasciculation

weakness



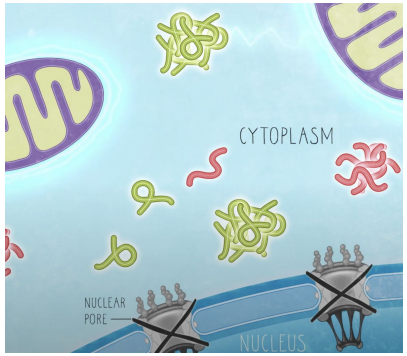
ETIOLOGY

- **Idiopathic** - most, 90% of the cases
- **Genetics** - 5-10%, mutation in > dozen genes
  - 25-40% defect in the *C9ORF72 gene:*
    - makes a protein in motor neurons and nerve cells in the brain
    - also in frontotemporal dementia (FTD)
  - 12-20% mutations in *SOD1* gene:
    - helps produce the enzyme copper-zinc superoxide dismutase 1
- **Environment** -
  - Toxic or infectious agents
  - Physical trauma
  - Viruses
  - Diet
  - Behavioral and occupational factors.



PATHOPHYSIOLOGY

- Nucleocytoplasmic transport defects
- Impaired proteostasis



Protein aggregates:

pathologic inclusions within neurons and glia.
(motor and nonmotor frontal and temporal cortical neurons and in more widespread areas - not classic ALS)

↓

Mitochondrial dysfunction

↓

Oxidative stress

↓

DNA repair

↓

Neuron death

Inclusion:

- Ubiquitin
- TAR DNA-binding protein (TDP-43)
- Fused in sarcoma (FUS) protein
- Optineurin

PATHOPHYSIOLOGY

- Transport defects

  Problem transport RNA in vesicle

  ↓

  Can't send message to target cell

- Cytoskeleton defects

  Axon retracts

  ↓

  Can't connect muscle

- Oligodendrocyte dysfunction

- Neuroinflammation and Astrogliosis

  Astrocyte & Microglia produces damaging factors to neuron

- Excitotoxicity

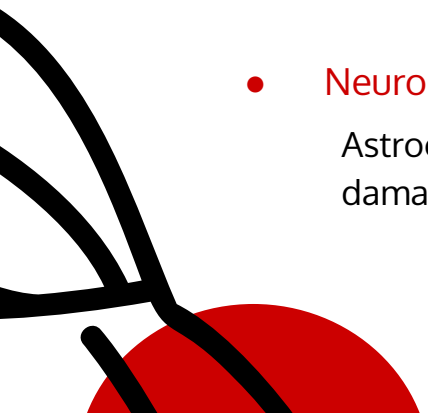
  Astrocyte reduce reuptake

  ↓

  Overactivation of receptors at synapse

  ↓

  Neuron death



SYMPTOMS

- Muscle **weakness**
- Muscle **stiffness** (spasticity)
- Muscle **twitches** - arm, leg, shoulder, tongue

"Bulbar onset" - begins in speech or swallowing

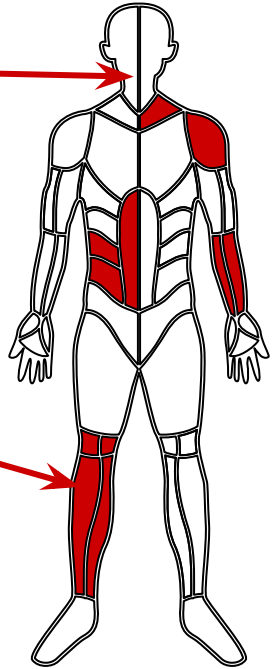
Bulbar: (more severe)

- Dysarthria
- Dysphagia
- Tongue atrophy & fasciculations
- Facial weakness & atrophy
- Pseudobulbar affect

Limb:

- Muscle cramps
- Painful neuropathy

"Limb onset" - begins in the arms or legs



- **Cognitive impairment:** Frontotemporal dementia
- **Autonomic** symptoms: constipation
- **Extrapyramidal** symptoms & signs of **Parkinsonism**

COMPLICATIONS

- Pneumonia
- Respiratory failure > Death

FACTS

01

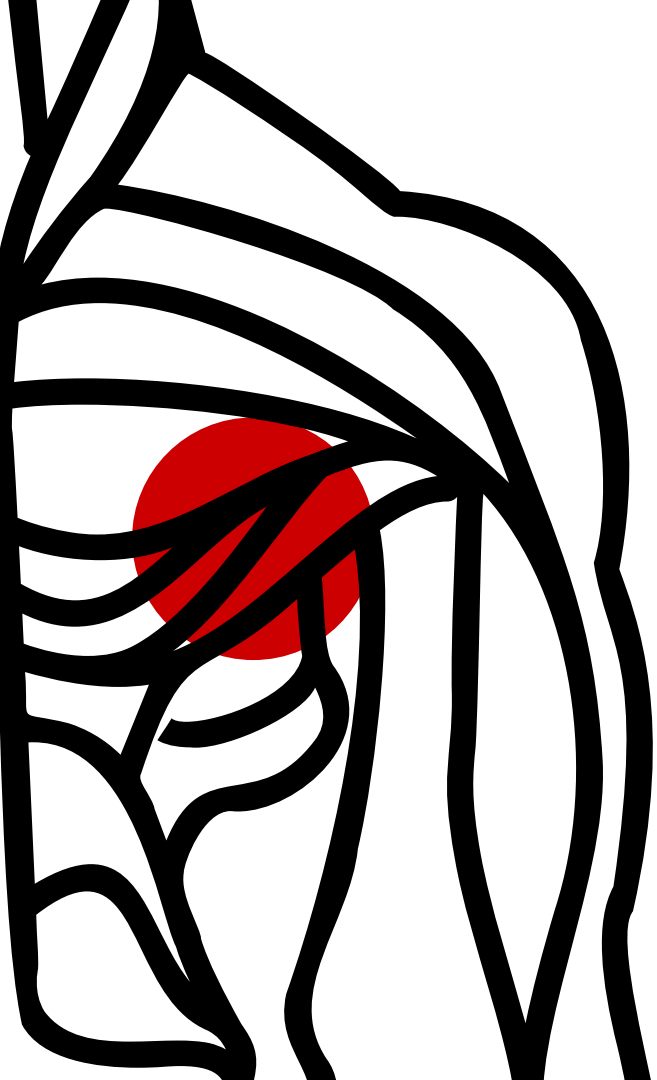
2-5 years average life expectancy (after symptoms)

02

10% survive 10 or more years

03

Once known as Lou Gehrig's disease (famous ballplayer)



RISK FACTORS

- **Age**: between 55-75 years old
- **Male**
- **Caucasians** and **non-Hispanics**

DIAGNOSIS

EMG

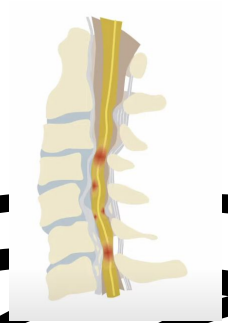
- Pattern:
  - Acute & chronic denervation
  - Reinnervation of muscles
- Fasciculations of tongue & lower extremities strengthens diagnosis

NCS

- rule out peripheral neuropathy
  - ex: multifocal motor neuropathy with conduction block

CT/MRI

- rule out cord disease/compression
  - Ex: Cervical spondylotic myelopathy (CSM)



Ultrasound Muscle

- detect fasciculations

Biopsy Muscle

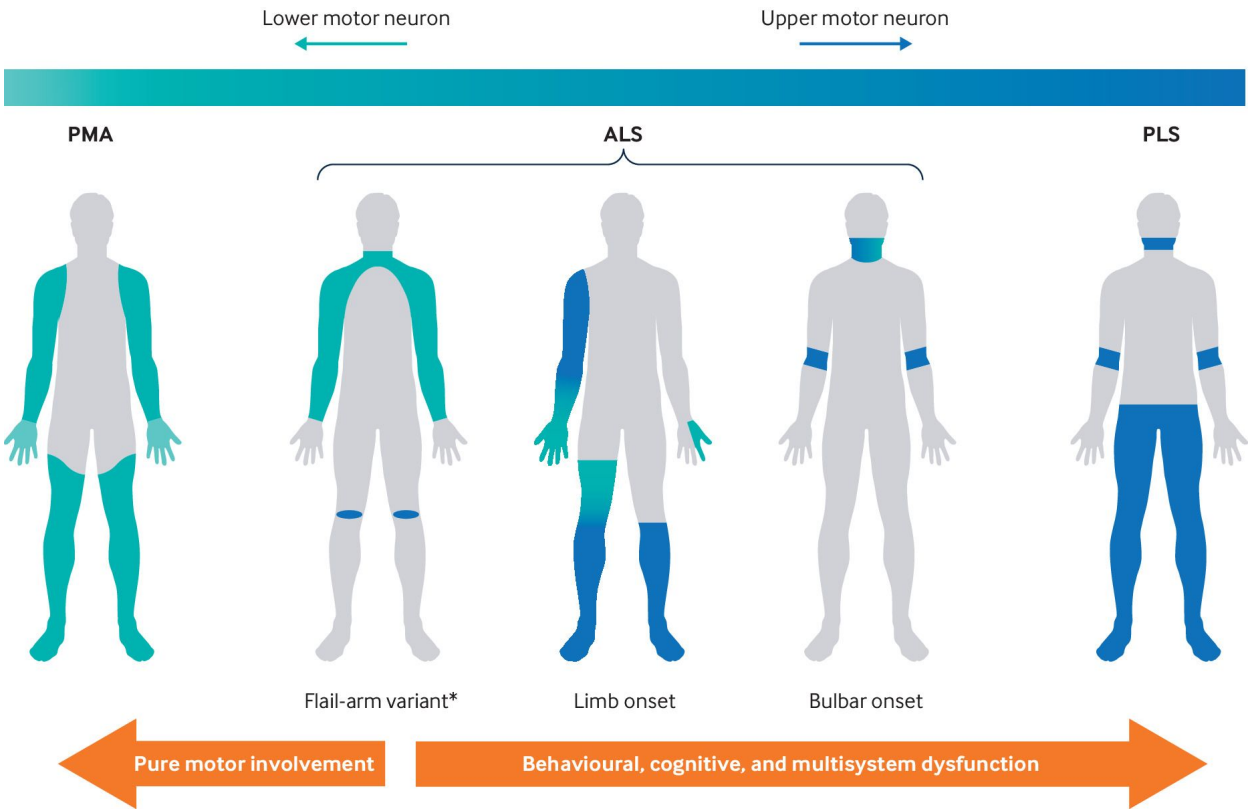
BLOOD TEST

- Exclude disorders mimicking ALS

MOTOR NEURON DISEASE

- **Amyotrophic Lateral Sclerosis:** UMN +LMN
- **Primary lateral sclerosis (**progressive pseudobulbar palsy): UMN
- **Progressive muscular atrophy** (progressive bulbar palsy): LMN asymmetrical
- **Spinal muscular atrophy**: LMN symmetrical >> in pediatrics

- **Flail arm syndrome:** LMN
- **Flail leg syndrome:** LMN
- **ALS-plus syndrome:** UMN + LMN + other symptoms
- **Postpolio syndrome:** LMN

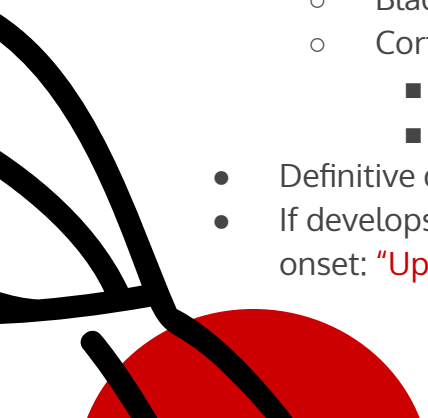


https://www.bmj.com/content/379/bmj-2022-073857

Primary lateral sclerosis

(progressive pseudobulbar palsy):

- UMN
- Slower progression
- Lower limb > torso > upper limb > bulbar
- Symptoms:
  - Loss of fluidity in gait
  - Spasticity
  - Hyperreflexia
  - Bladder instability and urinary retention
  - Corticobulbar symptoms:
    - Dysarthria
    - Pseudobulbar affect
- Definitive diagnosis 4 years after onset
- If develops LMN clinical signs after 4 years after onset: "Upper motor neuron-onset ALS"



Progressive muscular atrophy

(progressive bulbar palsy)

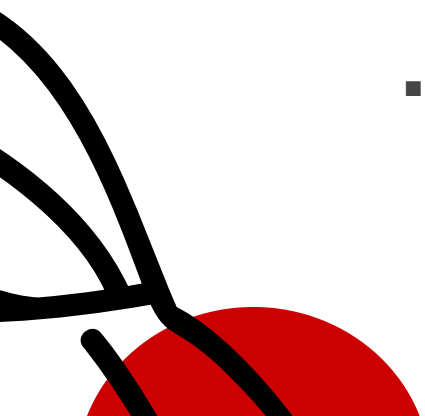
- LMN
- Prolonged survival than ALS
- Some develops UMN sign later : "Lower motor neuron-onset ALS"
- **Autopsy**: corticospinal tract abnormalities and TDP-43 positive inclusions in motor cortex

Spinal Muscular Atrophy

- LMN
- In Pediatrics
- Group of genetic disorder
  - Defects in:
    - SMN1 gene

	Onset
SMA type I (Werdnig-Hoffmann disease or infantile-onset SMA):	At birth
SMA type II (Dubowitz disease):	6-18 months
SMA type III (Kugelberg-Welander disease):	After 18 months
SMA type IV:	After 21 months

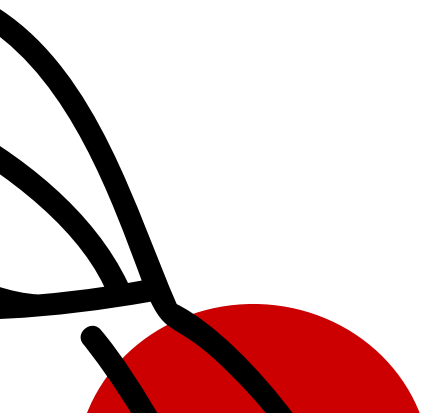
    - Androgen receptor gene on X chromosome
      - **Spinobulbar muscular atrophy** (Kennedy's disease): Adulthood



Flail arm syndrome

(brachial amyotrophic diplegia)

- LMN weakness and wasting
- Main: proximal arm
- begins proximally and spreads distally
- longer survival time & slower progression



Flail leg syndrome

(pseudo-polyneuritic variant of ALS/motor neuron disease)

- LMN weakness and wasting
- Main: distal leg
- lower rate of comorbid dementia
- longer survival time & slower progression

ALS-plus syndrome

- Clinical features of ALS with other disorders:
  - **Frontotemporal dementia (FTD)**
  - **Autonomic insufficiency**
  - **Parkinsonism**
  - **Supranuclear gaze paresis**
  - **Sensory loss**

TREATMENT

"NO Cure"

Pharmacologic

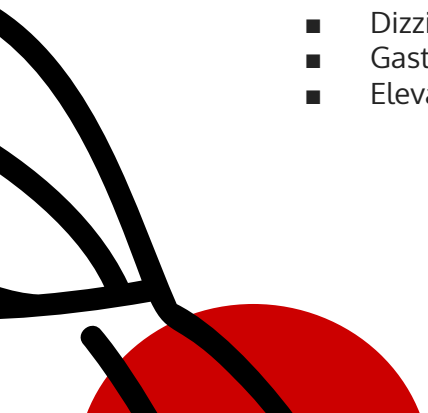
- **Riluzole**: slows progression
- **Edaravone**: reduces functional decline by 33% in early stage ALS
- **Symptomatic relief:**
  - **Sialorrhea**: Anticholinergic - TCA (ex: amitriptyline), sublingual atropine drops, parotid/submandibular Botox® (rare)
  - **Spasticity**: Baclofen
  - **Muscle cramp:** Muscle relaxant
  - **Pseudobulbar affect**: dextromethorphan/quinidine, TCA, SSRI

Non-Pharmacologic

- **Respiratory support:** Ventilators
- **Diet**:
  - High caloric diet
  - Early nutritional support (ex: percutaneous endoscopic gastrostomy tube)
- **Rehabilitation**
  - **Physical Therapy**
    - Low-impact aerobic exercises:
      - strengthen muscles
      - improve heart health
    - Stretching exercises:
      - prevent muscle stiffening.
  - **Occupational therapy**
  - **Speech therapy**
- **Psychosocial support**

Pharmacologic

- **Riluzole**: slows progression
  - Rilutek®
  - **Mechanism**:
    - inhibits glutamic acid release
    - noncompetitive block of N-methyl-D-aspartate (NMDA) receptor-mediated responses
    - direct action on the voltage-dependent sodium channel
  - **Dose**: 50 mg twice daily
  - **Side effects**:
    - Asthenia
    - Dizziness
    - Gastrointestinal disorders
    - Elevations in liver enzyme



- **Edaravone**: reduces functional decline in early stage ALS
  - Radicava®
  - **Mechanism:** free-radical scavenger that reduce oxidative stress
  - **Dose**:
    - 60 mg IV over 60 minutes OR
    - 105 mg (5 mL) oral suspension in the morning after overnight fasting
      - daily for 14 days > 14 days off treatment then **Subsequent treatment cycles**: daily for 10 days > 14 days off treatment
  - Side effects:
    - Injection-site contusion
    - Gait disturbance
    - Headache
    - Allergic reactions: Asthmatic attack

Non-Pharmacologic

- **Respiratory support:**
  - Serial assessment of **pulmonary function** every 3 months
    - Vital capacity (VC)
    - Maximal inspiratory pressure (MIP)
    - Maximal sniff nasal inspiratory force (SNIF)
      - avoids mouthpiece
      - better used than the VC or MIP for patients with bulbar weakness.
  - **Ventilators**
    - Criteria for **Noninvasive positive pressure ventilation (NPPV)**:
      - VC <50% OR
      - Orthopnea OR
      - SNIF <40 cm OR
      - MIP <60 cm OR
      - Abnormal nocturnal oximetry
    - **Invasive mechanical ventilation (IMV)** if long-term survival goal

THANK YOU

RESOURCES

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