Neurodegenerative disorders-1

Manar Hajeer, MD, FRCPath

University of Jordan, School of medicine

Different diseases

- **Involving the hippocampus and cortex**>>>> cognitive changes (memory, behavior and language disturbances) >>>> dementia >>>>>ALZHEIMER DISEASE (AD) , FRONTOTEMPORAL DEMENTIA (FTD), PICK DISEASE (SUBTYPE OF FTD)

- **Involving the basal ganglia** >>>>> movement disorders >>>>hypokinesia (PARKINSON DISEASE) or hyperkinesia (HUNTINGTON DISEASE)

- **Involving the cerebellum** >>>> ataxia >>> (SPINOCEREBELLAR ATAXIA, FRIEDRICH ATAXIA, ATAXIA TELANGECTASIA)

- **Involving the motor system** >>> difficulty swallowing and respiration with muscle weakness >> (Amyotrophic lateral sclerosis, spinal muscular atrophy)

Spinocerebellar degeneration:

- **Heterogeneous group of diseases.**
- **Differ in causative mutations, patterns of inheritance, age at onset, and signs and symptoms.**
- **Affects cerebellum along with spinal cord (commonly), other brain regions, and peripheral nerves variably.**
- **Clinical findings of cerebellar and sensory ataxia (loss of coordination), spasticity, and sensorimotor peripheral neuropathy.**

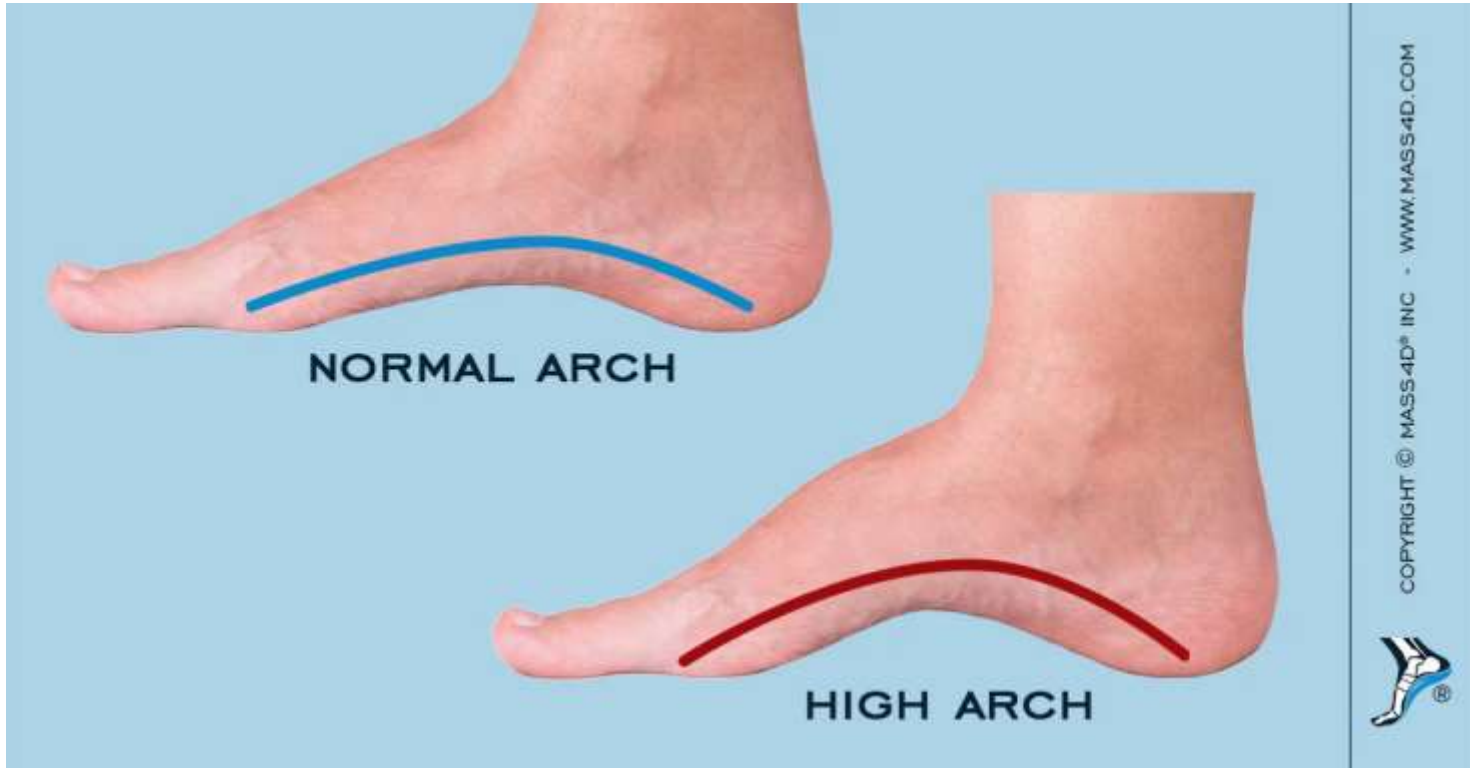
Spinocerebellar Ataxias

- **Applied to series of autosomal dominant diseases.**
- **Several subtypes that differ in symptoms that accompany the ataxia.**
- **Almost 45 distinct genetic subtypes have been identified.**
- **Several forms of SCA are caused by CAG repeat expansions (like HD), causing neuronal intranuclear inclusions.**
- **In these the age of onset decrease as the number of repeats increase.**

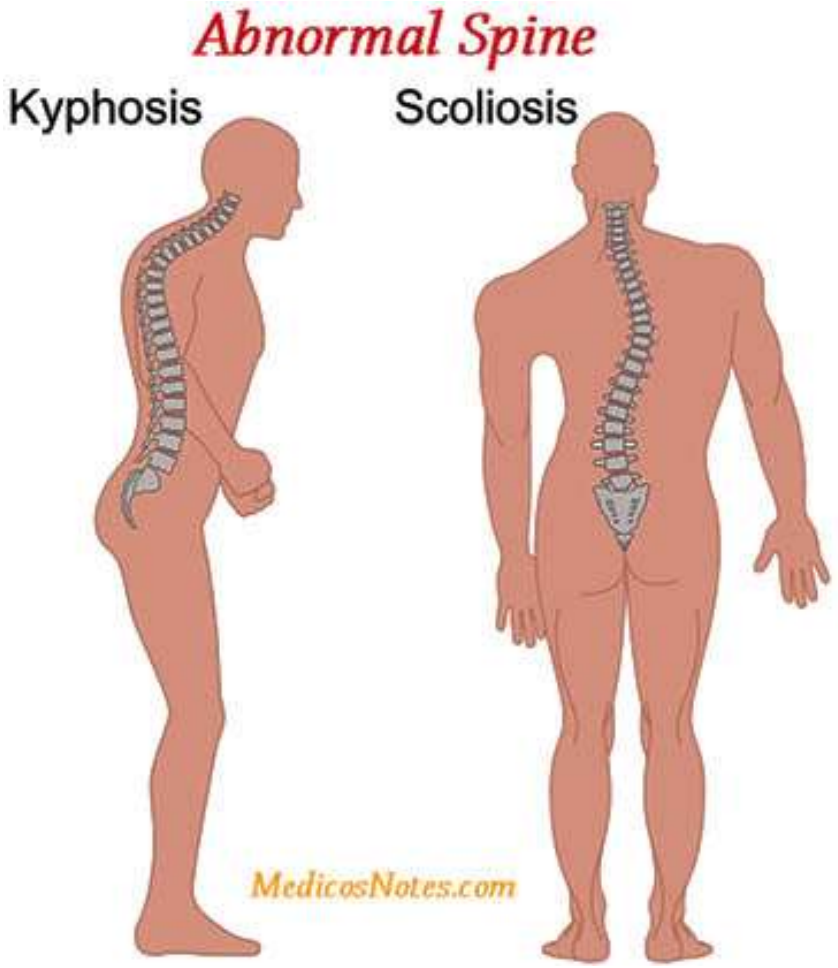
Friedreich ataxia

- **Autosomal recessive disorder.**
- **Manifest in the first decade of life.**
- **Gait ataxia, spasticity, weakness, sensory neuropathy, and a cardiomyopathy**
- **Followed by hand clumsiness and dysarthria (uncoordinated speech).**
- **Deep tendon reflexes are depressed or absent.**

- **Most patients develop Pes cavus and kyphoscoliosis.**
- **High incidence of cardiac disease and diabetes.**
- **Most patients become wheel chair bound within about 5 years of onset.**
- **Life expectancy is typically limited to 40 or 50 years of age.**



Pes cavus


Abnormal Spine
Kyphosis
Scoliosis
MedicosNotes.com

Mutations :

- **Caused by GAA trinucleotide repeat expansion.**
- **In the gene encoding Frataxin protein (regulates mitochondrial iron).**
- **Repeat expansion >> transcriptional silencing>> decreased frataxin>>mitochondrial dysfunction>>oxidative damage (ROS).**

- **The damage is not caused by the protein deposition. (loss of frataxin)**

Morphology:

- **Spinal cord shows loss of axons and gliosis in the posterior columns, the distal portions of corticospinal tracts, and the spinocerebellar tracts.**
- **Degeneration of neurons in the spinal cord, the brainstem, the cerebellum and of the motor cortex.**

- **Heart is enlarged.**

Ataxia telangectasia

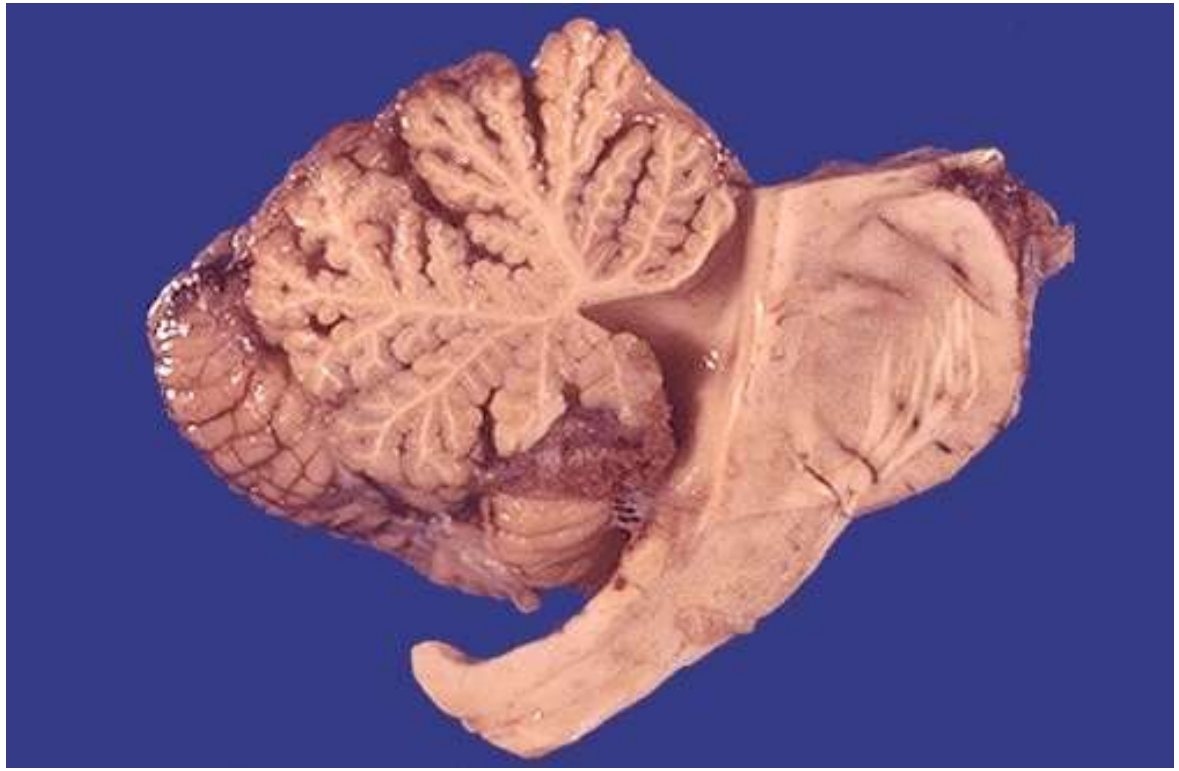
- **Autosomal recessive disorder.**
- **Ataxic dyskinetic syndrome beginning in early childhood.**
- **Recurrent sinopulmonary infections is common initial symptom.**
- **Later, speech become dysarthric with eye movement abnormalities.**
- **Development of telangiectasias in the conjunctiva and skin, along with immunodeficiency.**
- **Many affected individuals develop T cell leukemias.**

Pathogenesis:

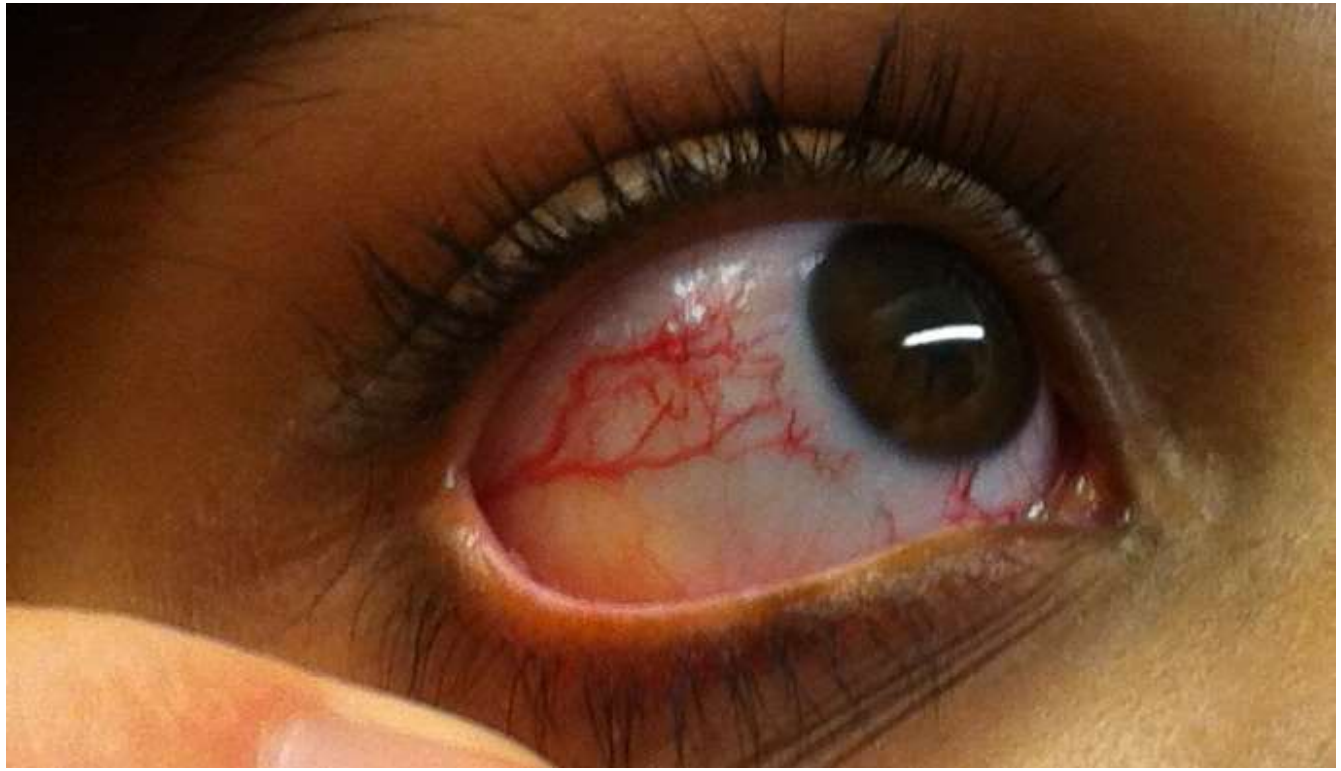
- **Affected gene: Ataxia telangiectasia mutated (ATM) gene on chromosome 11.**
- **Encodes a kinase with a critical role in the cellular response to double stranded DNA breaks (DNA repair).**

MORPHOLOGY

- **Abnormalities are predominantly in the cerebellum: loss of Purkinje and granule cells.**
- **Degeneration of the dorsal columns, spinocerebellar tracts, and anterior horn cells**
- **Peripheral neuropathy.**
- **Telangiectatic lesions are found in the CNS as well as in the conjunctiva and skin**



Cerebellar atrophy



Telangiectasia

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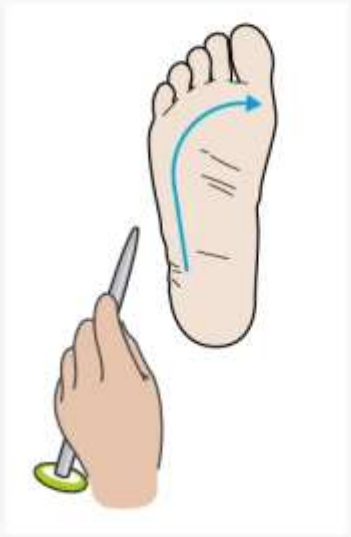
Amyotrophic Lateral Sclerosis

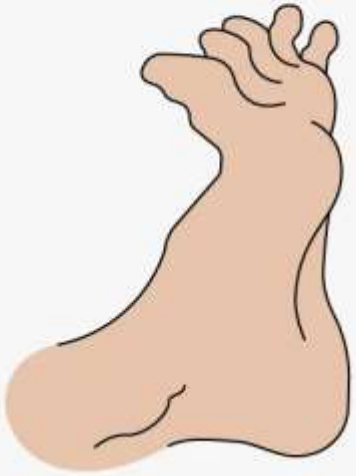
- **Death of lower motor neurons in the spinal cord and brain stem as well as upper motor neurons in the motor cortex.**
- **Loss of lower motor neurons results in denervation of muscles, muscular atrophy (amyotrophy), weakness, and fasciculations.**
- **Loss of upper motor neurons results in paresis, hyperreflexia, spasticity, along with a Babinski sign.**

The Babinski Reflex



test

negative



positive

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Cont’

- **Upper motor neuron loss >> Degeneration of the corticospinal tracts in the lateral portion of the spinal cord (lateral sclerosis, hardening)**
- **Sensation usually is unaffected, but cognitive impairment is not infrequent.**
- **Male predominance.**
- **5th decade and after.**

Clinical manifestations:

- Disease begin wit subtle asymmetric distal extremity weakness.
- Muscle strength and bulk diminish with progression.
- Fasciculations (involuntary contractions of individual muscle units)
- Involve respiratory muscles later leading to pulmonary infections.
- Most patients exhibits both upper and lower motor neuron disease.

- Bulbar amyotrophic lateral sclerosis : degeneration of the lower brain stem cranial motor nuclei. abnormalities of swallowing and speaking dominate.

Pathogenesis:

- **Most cases are sporadic, 10% are familial (AD, early onset).**
- **Mutations in the superoxide dismutase gene, *SOD1,* on chromosome 21.**
- **Generate abnormal misfolded SOD1 protein >>> trigger the unfolded protein response >>>> apoptotic death of neurons.**

- **OTHER MUTATIONS:**
- **Hexanucleotide repeat expansion of C9orf72 (familial forms)**
- **TDP43 (also associated with FTLD).**

- **Genetic and clinical overlap with FTLD.**

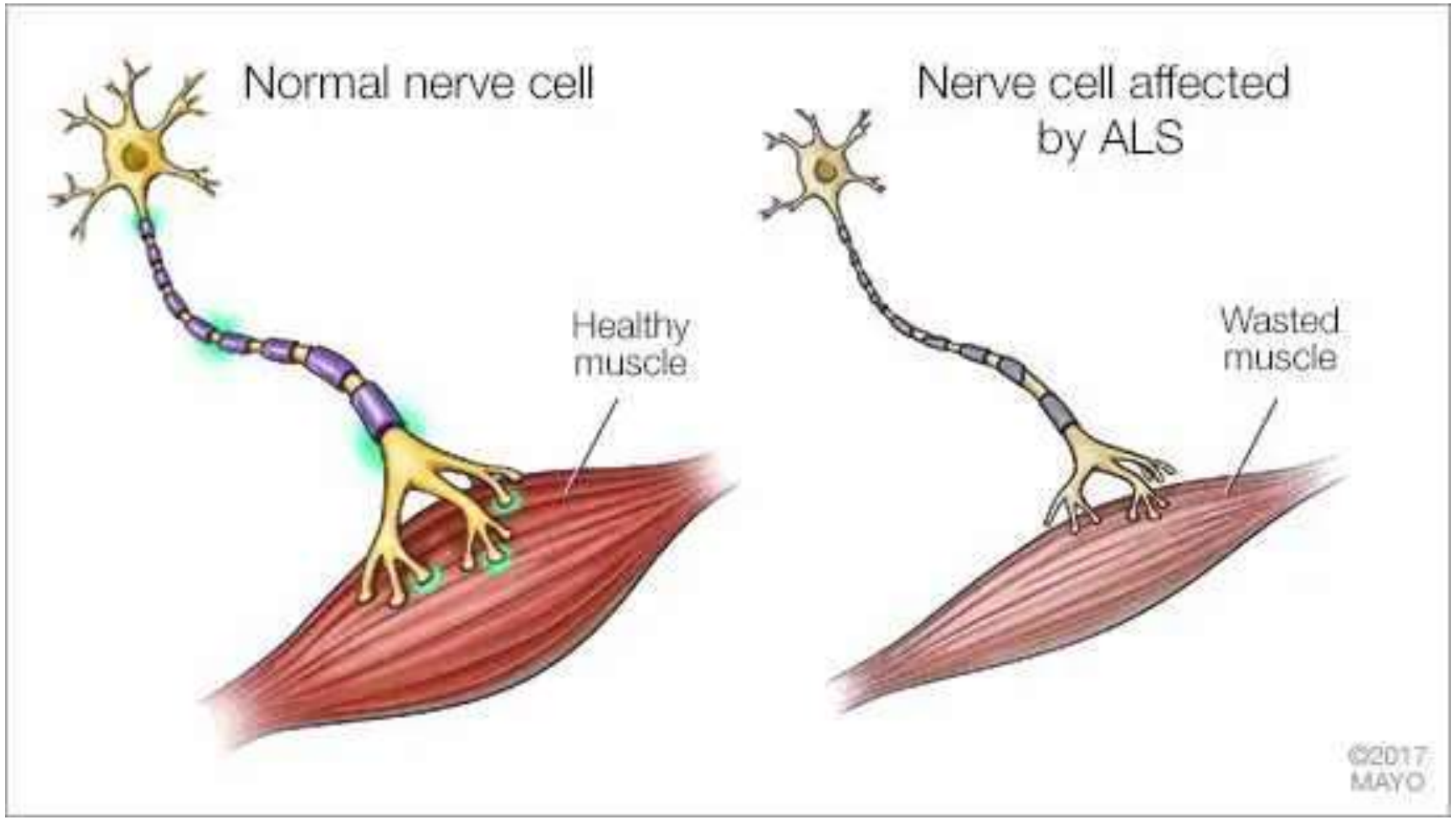
Morphology:

- **MACROSCOPY:**

- **Anterior roots of the spinal cord: thin and grey (most striking).**
- **In severe cases: atrophy of precentral gyrus (motor cortex)**

Microscopy:

- Reduction in number of anterior horn neurons (throughout the spinal cord)
- Reactive gliosis and loss of anterior root myelinated fibers.
- Similar changes in motor cranial nerve nuclei.
- Sparing of those supplying the extraocular muscles.
- Cytoplasmic inclusions that contain TDP43 in some cases.
- Skeletal muscles show neurogenic atrophy


Normal nerve cell
Healthy muscle
Nerve cell affected by ALS
Wasted muscle
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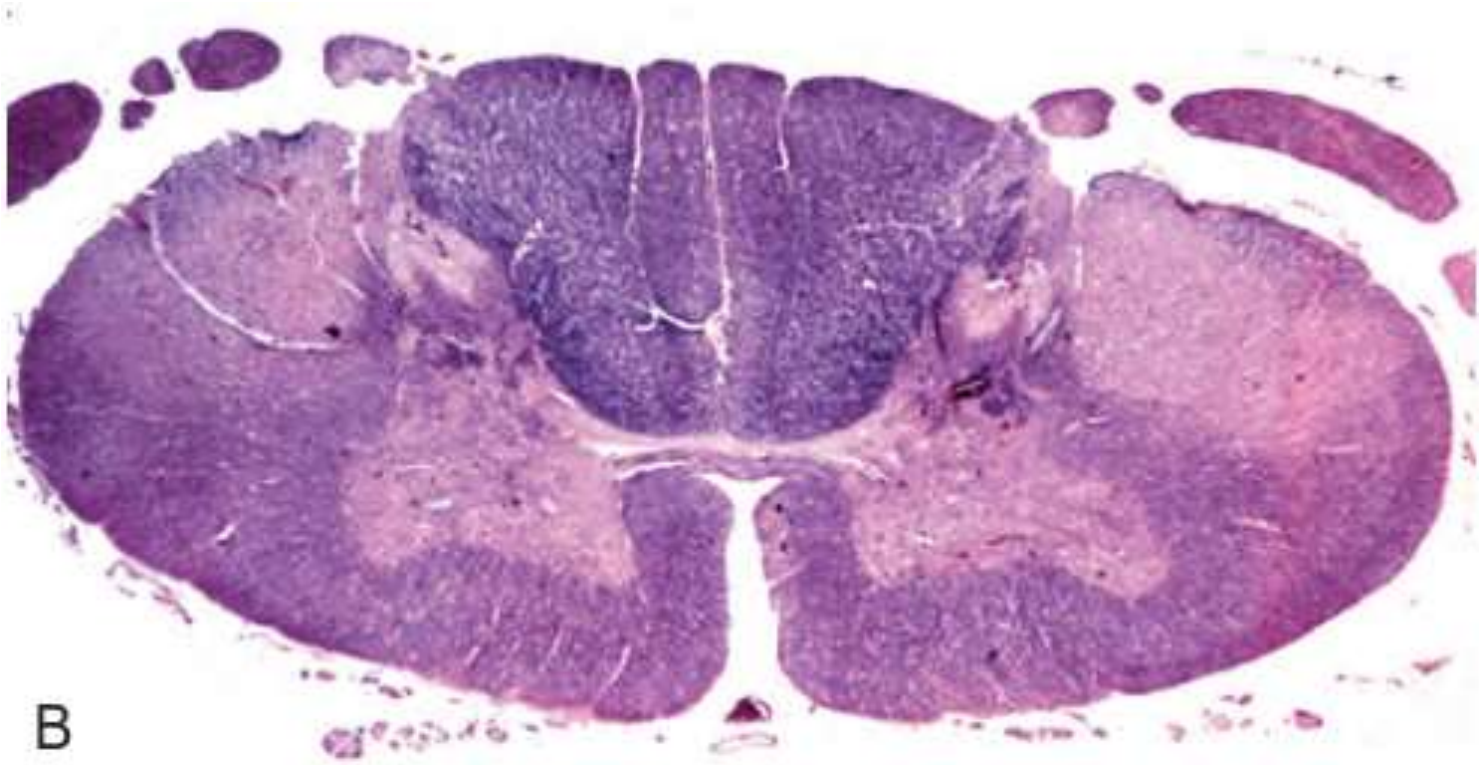
- Loss of anterior horn cells>> (ventral) spinal motor nerve roots demonstrate **atrophy**, as seen here in comparison with **normal** ventral spinal cord nerve roots.



Loss of myelinated fibers (lack of stain) in corticospinal tract.

Spinal muscular atrophy (SMA)

- **Genetically linked disorders of childhood.**
- **Marked loss of lower motor neurons**
- **Results in progressive weakness.**
- **SMN1 gene loss of function mutation.**

- **The most severe form with the earliest onset:**
  - **SMA type I, Werdnig Hoffmann disease**
  - **Onset during the first year of life**
  - **Death typically within 2 years**