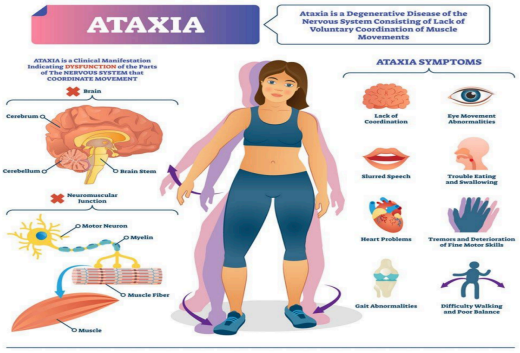
Rawan Mohammed

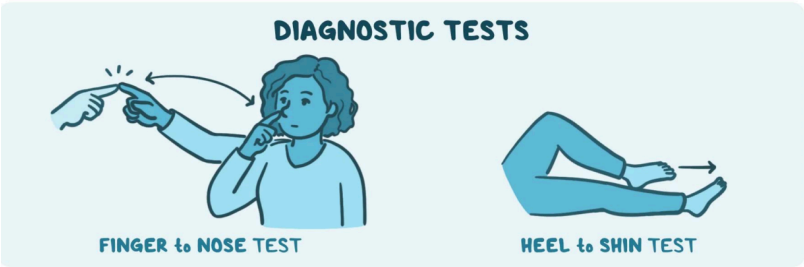
Lecture 3:

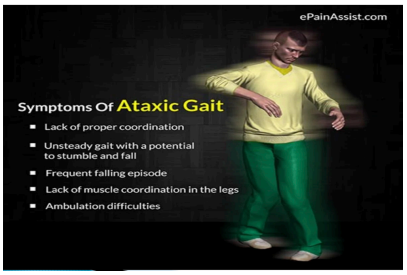
Involving the cerebellum → ataxia → (SPINOCEREBELLAR ATAXIA, FRIEDREICH ATAXIA, ATAXIA TELANGIECTASIA)

Spinocerebellar Ataxia:

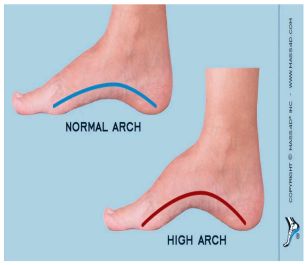


- **Heterogeneous** group of diseases, characterized by **cerebellar** and **sensory ataxia**, spasticity, and sensorimotor peripheral neuropathy.
- Differ in causative mutations, patterns of inheritance, age at onset, and signs and symptoms.
- Affects cerebellar cortex, spinal cord, other brain regions, and peripheral nerves variably.
- Several forms of SCA are caused by CAG repeat expansions (like HD), causing intranuclear inclusions, among other mutations.





Friedreich Ataxia:

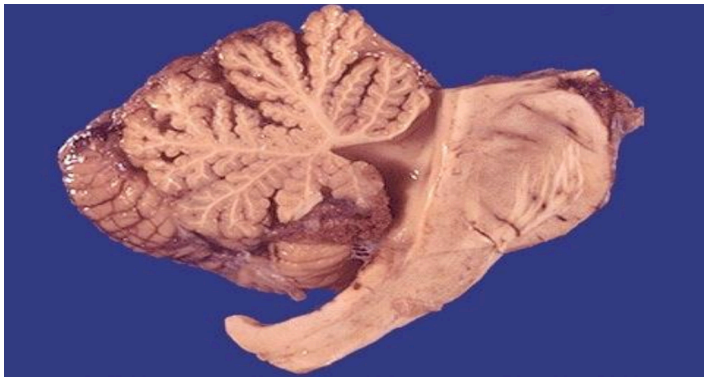


- Most important SCA.
- Autosomal recessive disorder.
- First decade of life.
- Gait ataxia, followed by hand clumsiness and
- dysarthria.
- Pes cavus and kyphoscoliosis.
- High incidence of cardiac disease and diabetes.

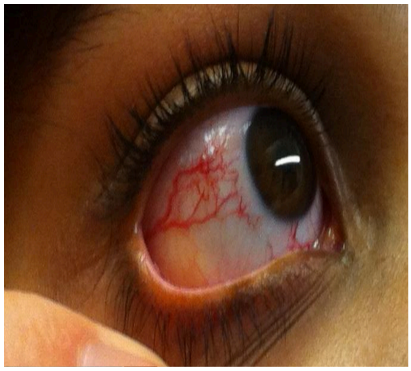
Mutations:

- **GAA trinucleotide** repeat expansion.
- **Frataxin** protein (**regulates mitochondrial iron**).
- **Transcriptional silencing** → decreased frataxin→mitochondrial dysfunction→**oxidative damage** (ROS).
- The damage is **not** caused by the protein deposition. (**loss of frataxin**)

Ataxia Telangiectasia:



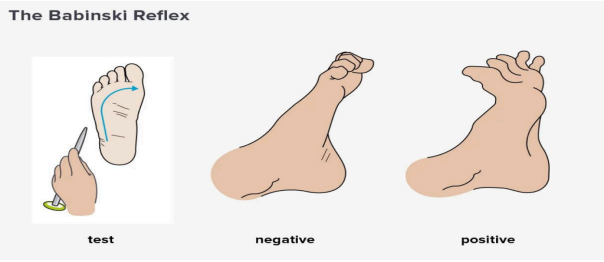
Cerebellar Atrophy



Telangiectasia

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**.
- 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



Pathogenesis

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

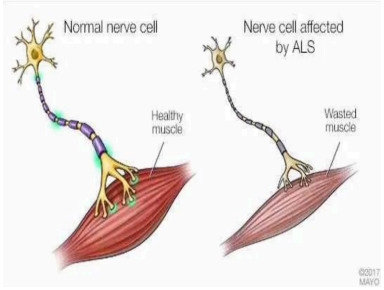
OTHER MUTATIONS:

- Hexanucleotide repeat expansion of **C9orf72** (familial forms)
- **TDP43** (also associated with **FTLD**)
- **FUS** gene.
- **Genetic and clinical overlap with FTLD.**

Symptoms:

- Begins with subtle asymmetric distal extremity weakness.
- As the disease progresses, muscle strength and bulk diminish.
- Involuntary contractions of individual motor units (fasciculations)
- Eventually involves the respiratory muscles >>> recurrent bouts of pulmonary infection (the usual cause of death).
- Most patients exhibit both upper and lower motor neuron disease.
- Bulbar amyotrophic lateral sclerosis : degeneration of the lower brainstem cranial motor nuclei. abnormalities of
- swallowing and speaking dominate.

Morphology:

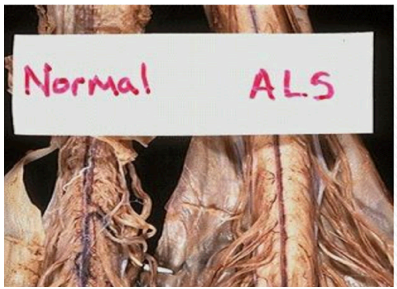


Macroscopy:

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

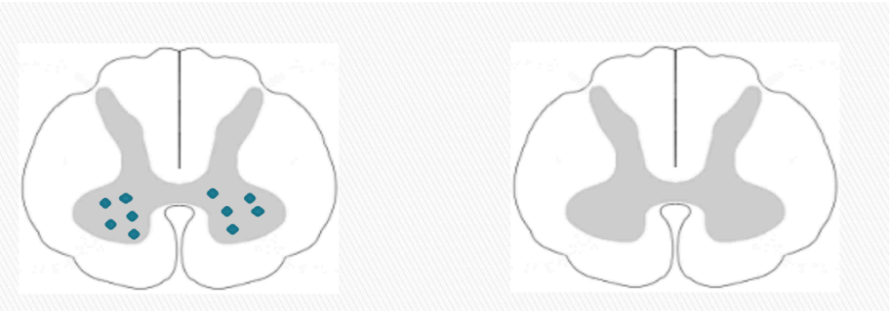
Microscopy:

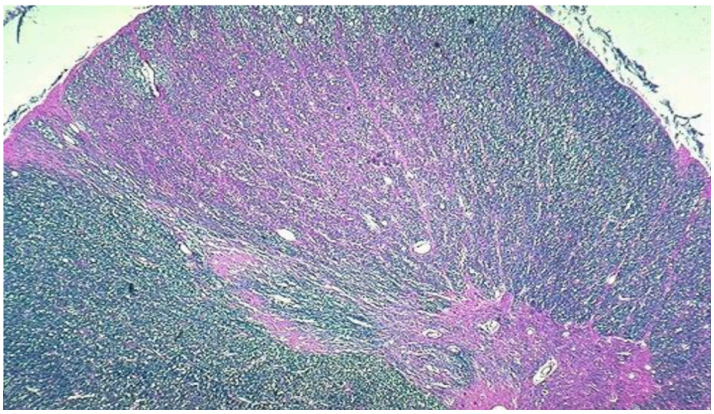
- Reduction in number of anterior horn neurons (throughout the spinal cord)
- Reactive gliosis and loss of anterior root myelinated fibers.
- Similar changes in motor cranial nerve nuclei.
- Sparing of those supplying the extraocular muscles.
- Cytoplasmic inclusions that contain TDP43.
- Skeletal muscles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



- Loss of anterior horn cells→ (ventral) spinal motor nerve roots demonstrate atrophy, as seen here in comparison with normal ventral spinal cord nerve roots

Normal
Vs ALS





Lateral Column Degeneration with ***Gliosis****- the “sclerosis” of ASL*

Disease	Clinical Pattern	Protein Inclusions
Alzheimer disease (AD)	Dementia	Aβ (plaques) Tau (tangles)
Frontotemporal lobar degeneration (FTLD)	Behavioral changes, language disturbance	Tau TDP43 Others (rare)
Parkinson disease (PD)	Hypokinetic movement disorder	α-synuclein Tau
Huntington disease (HD)	Hyperkinetic movement disorder	Huntingtin (polyglutamine repeat expansions)
Spinocerebellar ataxias	Cerebellar ataxia	Various proteins (polyglutamine repeat expansions)
Amyotrophic lateral sclerosis (ALS)	Weakness with upper and lower motor neurons signs	SOD1 TDP43

Acquired Metabolic and toxic disturbances

Common causes of neurologic illnesses.
Brain is particularly vulnerable because of its high metabolic demands.

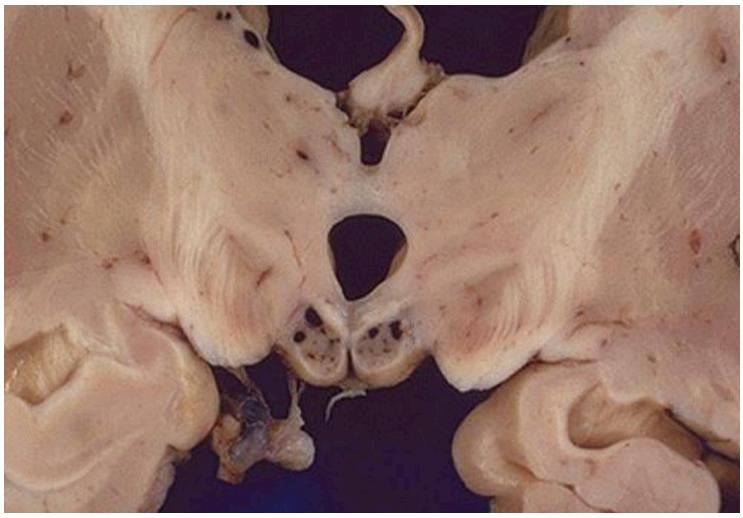
Nutritional diseases:

Thiamine Deficiency:

- **Chronic alcoholism**, gastric disorders, gastric **bypass surgery**, or persistent **vomiting**.
- **Beriberi** (systemic manifestations)
- **Wernicke encephalopathy**
- Abrupt onset of confusion
- **Ataxia**
- Abnormalities in eye movement
- **Tx:**
  - thiamine **reverses** deficits.
  - **Delayed Tx:** irreversible profound memory disturbance (**Korsakoff syndrome**)
  - **Wernicke-Korsakoff syndrome**

Morphology:

- Foci of hemorrhage and necrosis (mammillary bodies & adjacent to the **3rd** and **4th** ventricles).
- later, cystic space with **hemosiderin-laden macrophages**.
- **Medial dorsal nucleus** of thalamus lesions best correlates with the memory disturbance in **Korsakoff syndrome.**



Vitamin B12 Deficiency

- Anemia + neurologic deficits.
- Subacute combined **degeneration** of the spinal cord.
- Ascending and descending tracts of the spinal cord are affected.
- Symptoms develop over weeks.
- Early clinical signs:
  - Mild **ataxia**
  - lower-extremity numbness and tingling.
  - Can progress to spastic weakness of the lower extremities
  - **Complete paraplegia** (poor outcome despite Tx)

Hypoglycemia

- The Effects resemble those of global hypoxia (**anoxia**).
- Energy substrate (glucose).
- **Hippocampal neurons** are particularly **susceptible**.
- **Cerebellar Purkinje** cells are relatively **spared**.
- If level and duration of hypoglycemia are sufficiently severe → **widespread injury**.

Hyperglycemia

- Uncontrolled diabetes mellitus.
- **Ketoacidosis** or **hyperosmolar coma.**
- Confusion, stupor, and eventually coma.
- Intracellular **dehydration**.
- Rapid correction can produce severe cerebral edema (correct **gradually**).

Hepatic Encephalopathy:

- Hepatic dysfunction leads to depressed levels of consciousness or coma.
- Early stages: flapping tremor “asterixis”.
- Elevated levels of ammonia, inflammation and hyponatremia.
- Ammonia metabolism occurs only in astrocytes **“glutamine synthetase”**
- (**Alzheimer type II cells)**: **astrocytes** in the cortex and basal ganglia with **swollen** pale nuclei

Ethanol

- **Acute** intoxication is **reversible**.
- Excessive intake leads to profound metabolic disturbances (**brain swelling** and death)
- Chronic alcoholism : cerebellar dysfunction,1% of cases, (atrophy in the anterior vermis):
  - **Truncal ataxia**
  - **Unsteady gait**
  - **Nystagmus.**