PATHOLOGY

SHEET NO. 3

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بسم الله الرحمن الرحيم

[the black and red is the slides content and the blue is the doctor's notes]

❖Neurodegenerative disorders-3

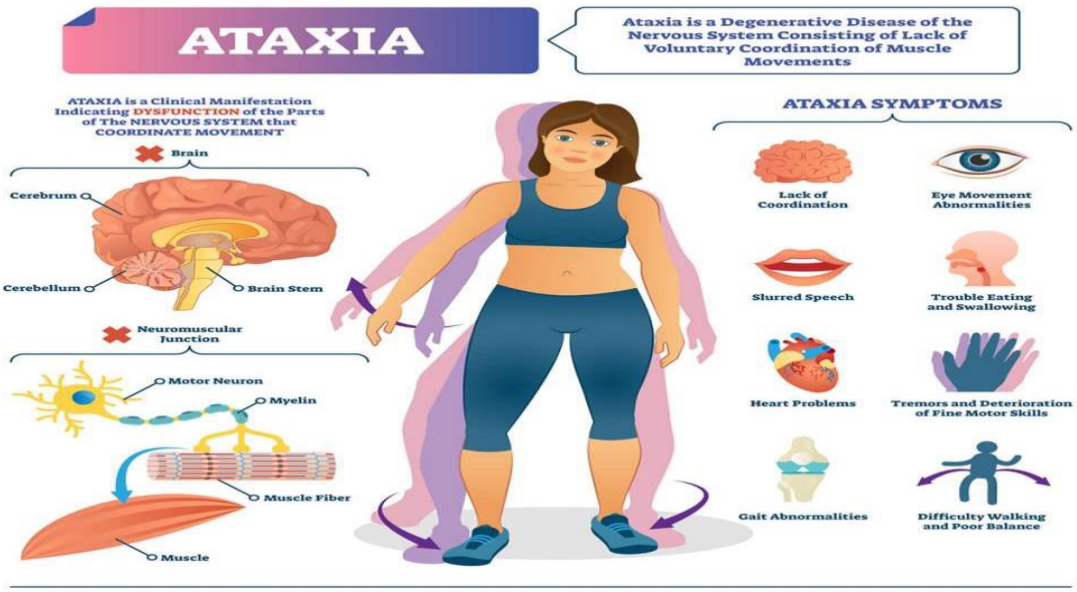
-in this lecture we will talking about:

1. the cerebellum disorders >>>> ataxia >>> (SPINOCEREBELLAR ATAXIA, Friedrich ataxia, ataxia telangectasia)
2. the motor system disoreders >>> difficulty swallowing and respiration with muscle weakness >> (AMYOTROPHIC LATERAL SCLEROSIS).
3. Acquired metabolic and toxic disturbances.

1-cerebellum diseases:

A. <u>spinocerebellar ataxias:</u>

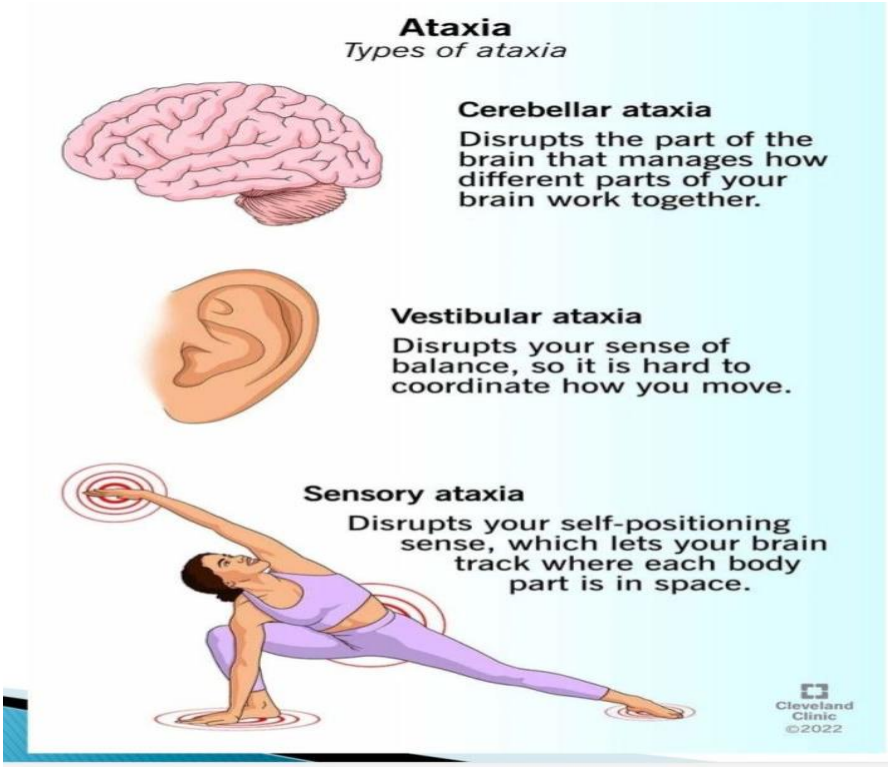
- Heterogeneous group of diseases, characterized by cerebellar and sensory ataxia, spasticity, and sensorimotor peripheral neuropathy.
- Differ in causative mutations, patterns of inheritance, age at onset, and signs and symptoms.
- Affects cerebellar cortex, spinal cord, other brain regions, and peripheral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

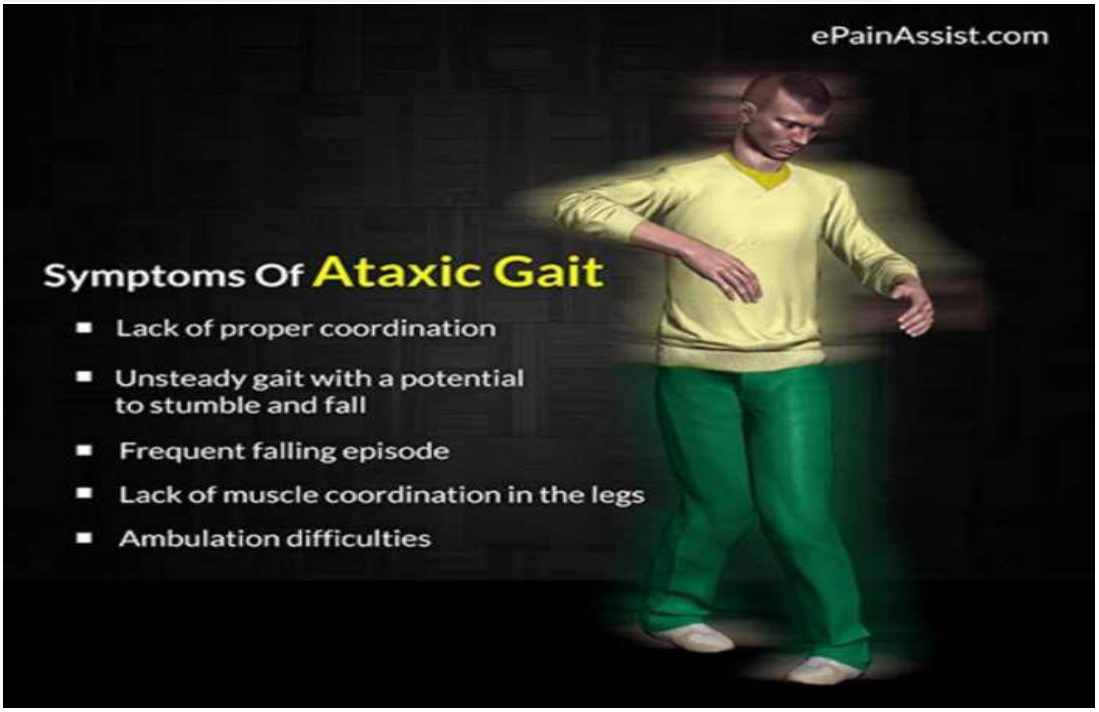


-the types of ataxia:

1. Cerebellar ataxia
2. Vestibular ataxia
3. Sensory ataxia

The main difference between cerebellar ataxia and sensory ataxia is the sensory ataxia get worse when the patient closes his eyes and when the doctor asks him to close his eyes and walk he will fall.

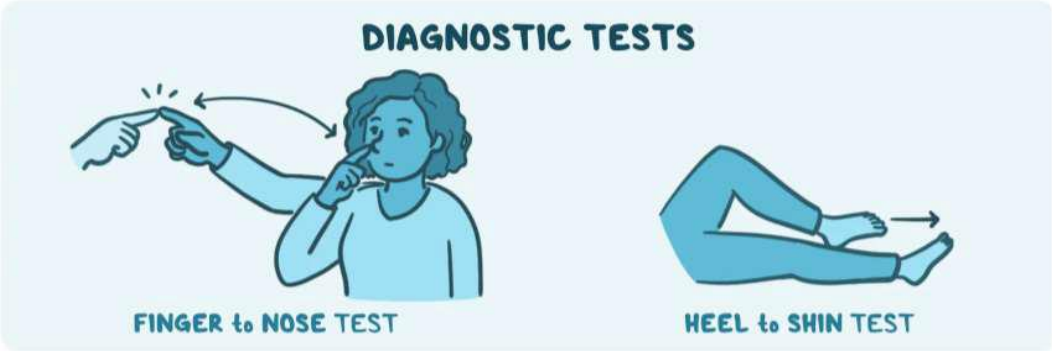




- The tests that measure coordination:

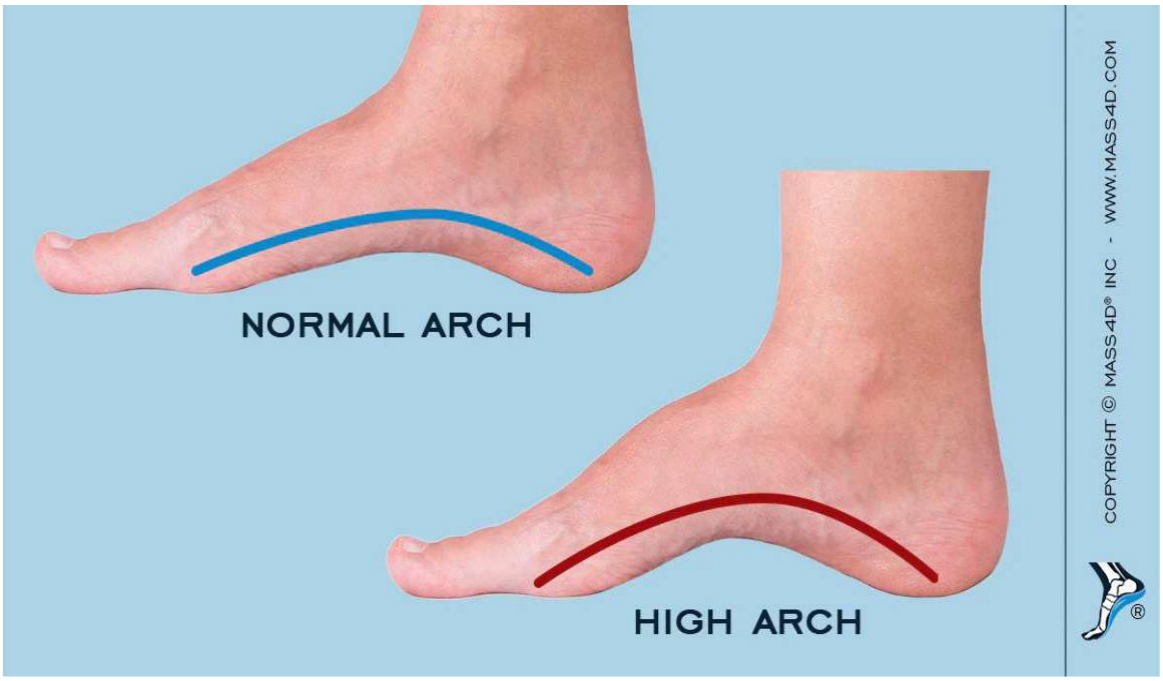
a. Finger to nose test

b. Heel to shin test



B. <u>Friedreich ataxia:</u>

- Most important SCA.
- Autosomal recessive disorder.
- First decade of life.
- Gait ataxia, followed by hand clumsiness and dysarthria (slurred speech).
- Pes cavus and kyphoscoliosis. (symptoms out of disease domain)
- High incidence of cardiac disease and diabetes. (Those patients may die earlier due to hypertrophic cardiac myopathy that cause sudden death).
- Young age is the guiding clue.

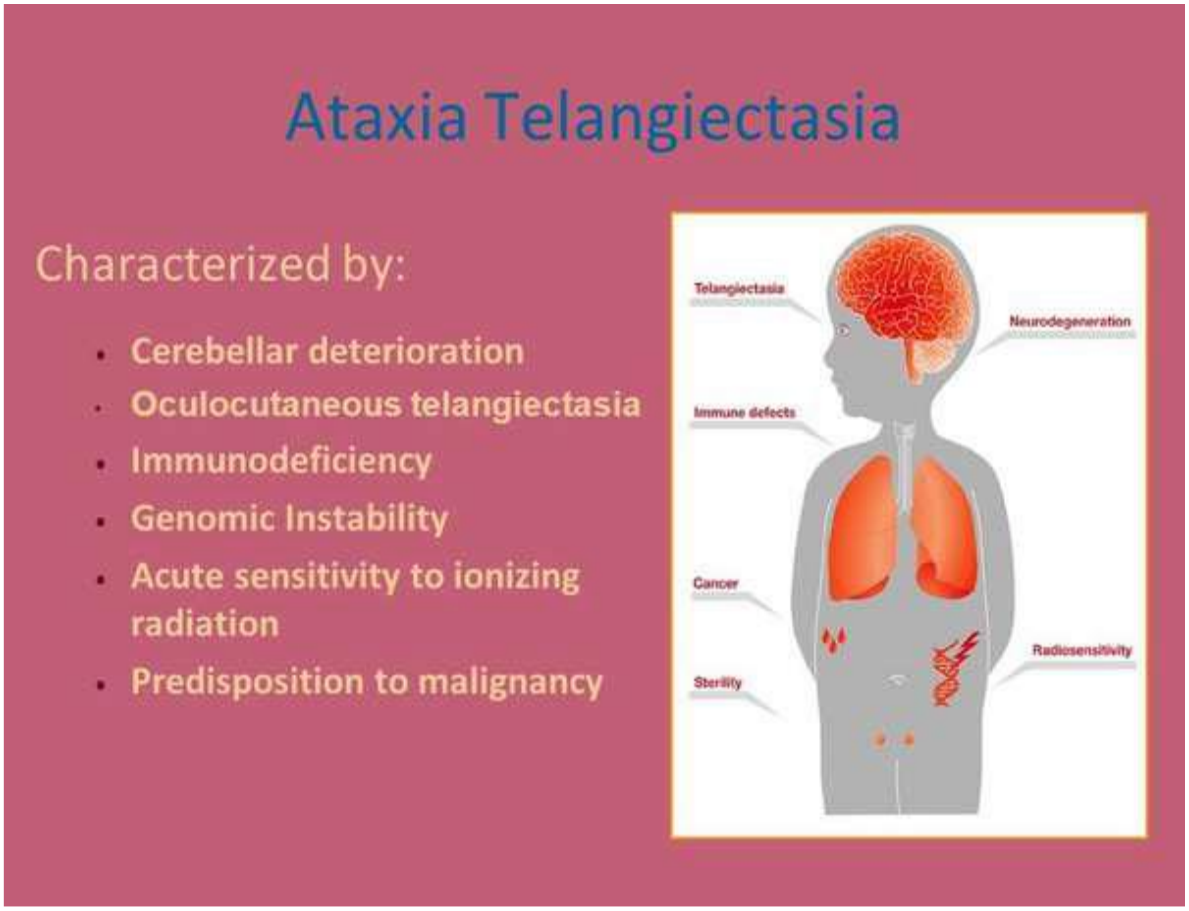


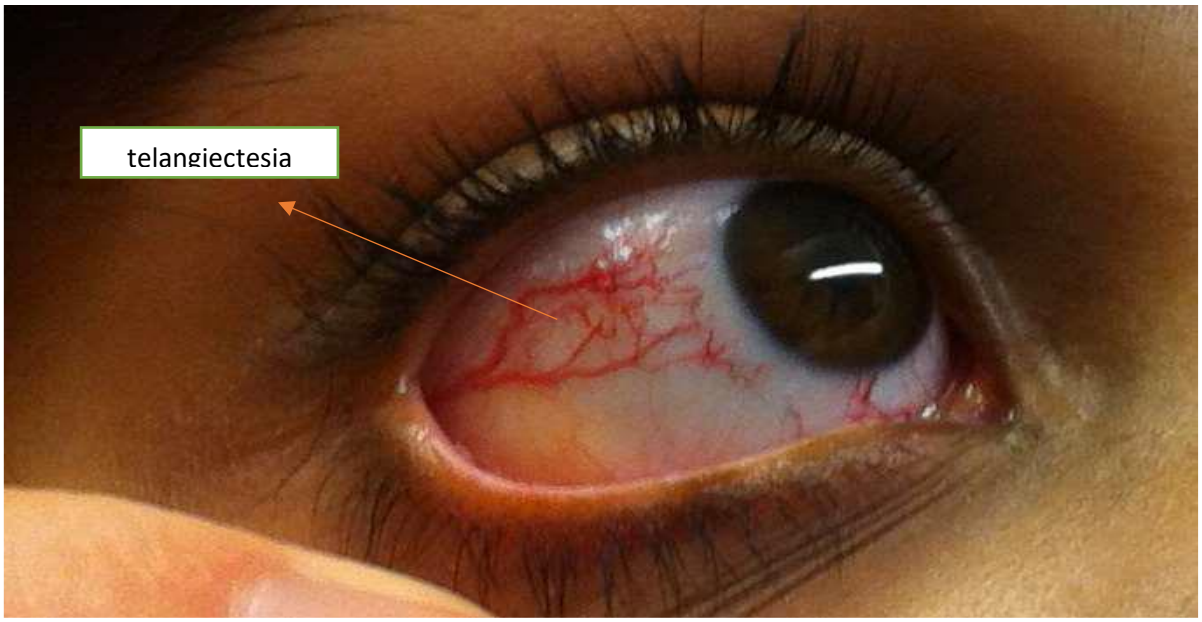
-the mutation that cause friedreich ataxia:

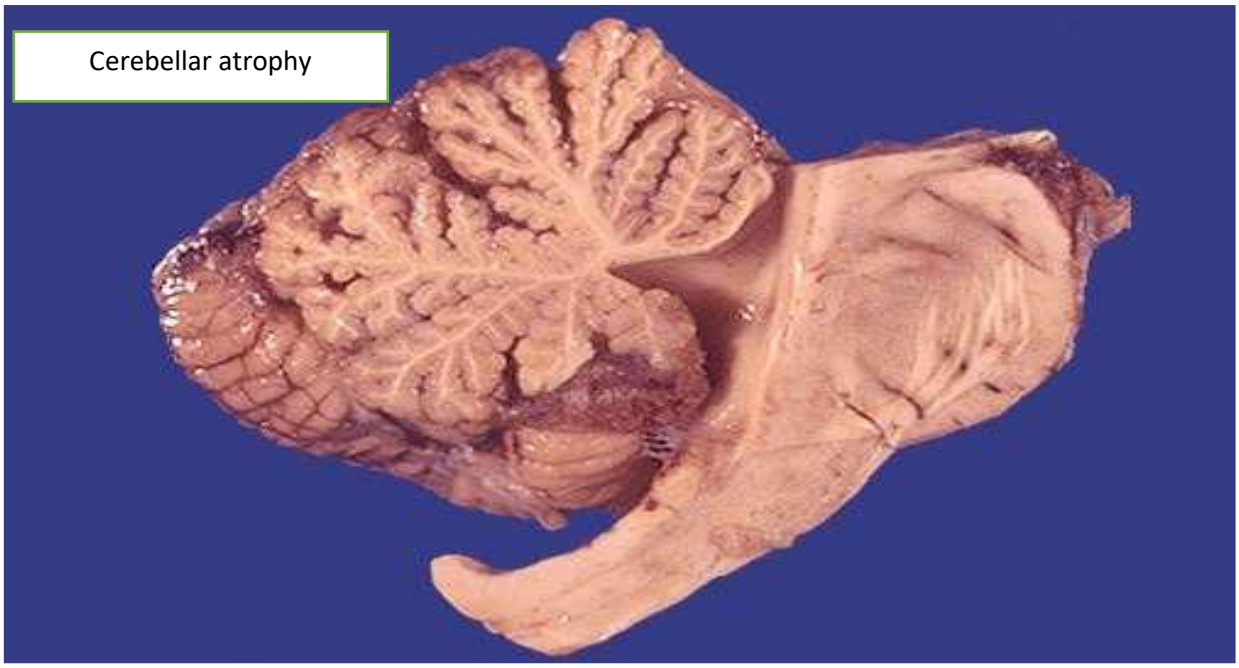
- GAA trinucleotide repeat expansion.
- Frataxin protein that coded by GAA (regulates mitochondrial iron).
- Transcriptional silencing >> decreased frataxin>>mitochondrial dysfunction>>oxidative damage (ROS).
- The damage is not caused by the protein deposition. (loss of frataxin)
- . this repeat leading to silence mutation this mutation prevents frataxin protein transcription which's lead to decrease regulation for iron and ineffective oxidative phosphorylation that result to ROS production that cause cell damage SO THE DAMAGE NOT CAUSED BY PROTEIN ACUMMULATION it's by loss of frataxin protein.

C. <u>Ataxia telangiectasia:</u>

- Telangiectasia means dilated a small blood vessel.
- It's inherited.
- It causes cerebellar atrophy.
- Young age + telangiectasia is the guiding clue.







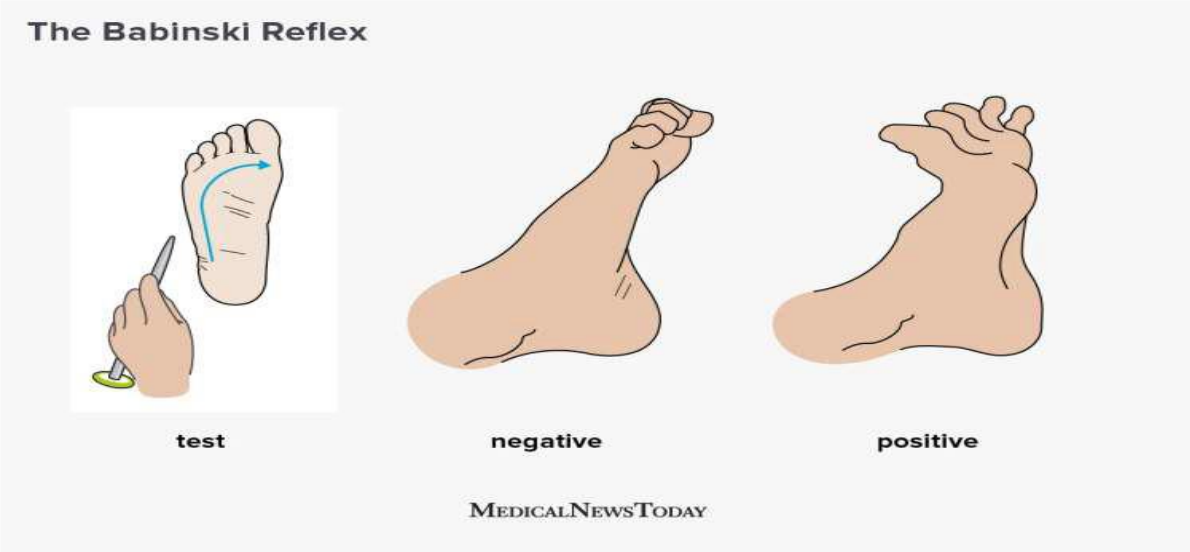
2-motor system disease:

a) Amyotrophic lateral sclerosis:

-Amyotrophic means no nutrition to muscles.

-lateral sclerosis means hardening of columns of spinal cords due to degeneration.

- 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 fasiculations.
- Loss of upper motor neurons results in paresis, hyperreflexia, spasticity, along with a Babinski sign.
- Negative Babinski sign ~~flexion~~ ~~normal~~
- Positive Babinski sign ~~hyperreflexion~~ ~~abnormal~~



- 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.
- 5thdecade and after**.**

-pathogenesis of Amyotrophic lateral sclerosis:

- 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 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.

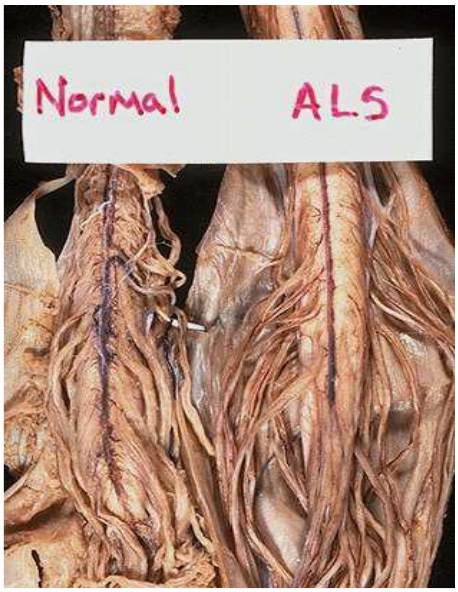
-Morphology :

Macroscopy

-Anterior roots of the spinal cord (most striking): thin and gray.

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

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.

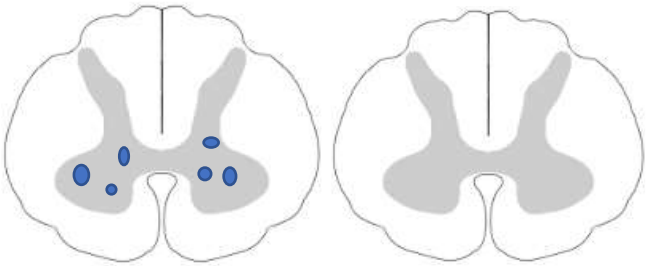
-Sparing of those supplying the extraocular muscles.

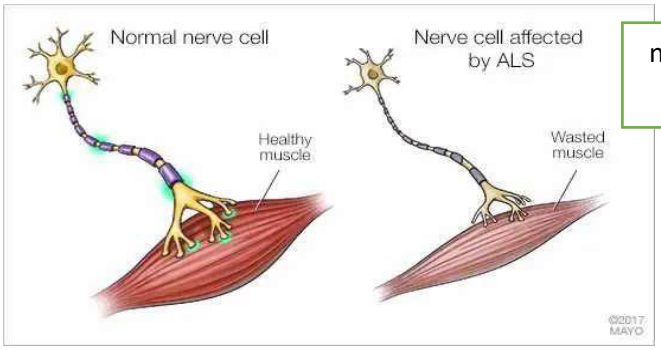
-Cytoplasmic inclusions that contain TDP43.

-Skeletal muscles show neurogenic atrophy.

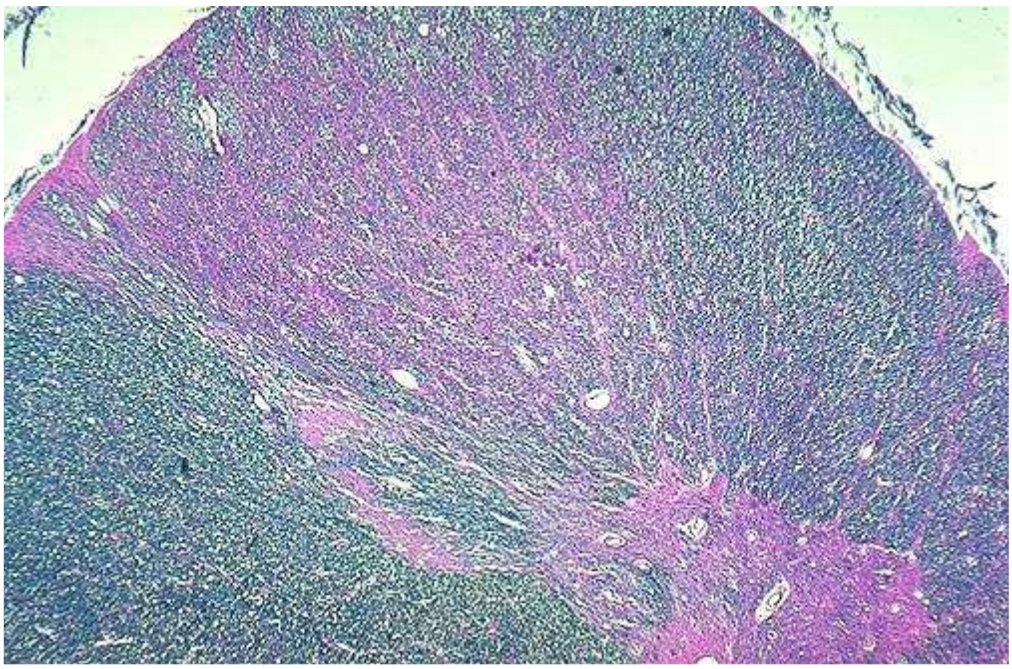
Normal

ALS





neurogenic atrophy.



LATERAL COLUMN DEGENERATION WITH GLIOSIS (sclerosis of ALS)

The doctor said she won't ask about this pic in exam

Table 23.3 Features of the Major Neurodegenerative Diseases

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

Summarize it

3-Acquired metabolic and toxic disturbances.

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

a. Nutritional diseases:

-Thiamine Deficiency:

- Chronic alcoholism, gastric disorders, gastric
- bypass surgery, or persistent vomiting.
- **Beriberi (systemic manifestations)**
- **Wernicke encephalopathy**

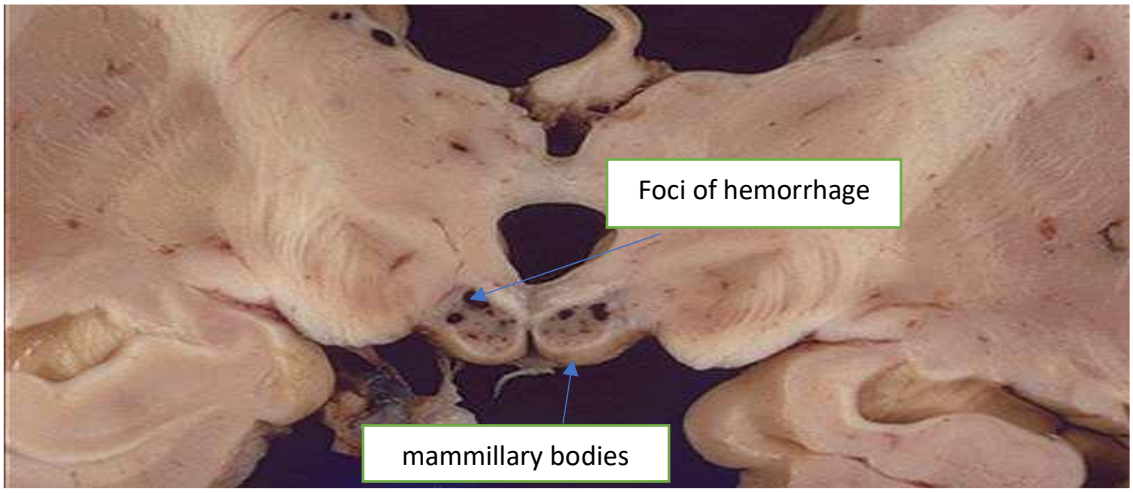
-the features of Wernicke encephalopathy:

1. Abrupt onset of confusion
2. Ataxia.
3. Abnormalities in aye movement(nystagmus)

- Tx:thiamine reverses deficits.
- Delayed Tx cause irreversible profound memory disturbance (Korsakoff syndrome)
- Wernicke-Korsakoff syndrome. ⟷ Thiamine Deficiency

-**Morphology**:

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



-V b12 deficiency:

-cuased by :

1. gastric bybass.
2. gastritis .
3. in those who have antibodies to intrinsic factor .

- ❖ Anemia + neurologic deficits.
- ❖ **Subacute combined degeneration of the spinal cord**. [Very important]
- ❖ Ascending and descending tracts of the spinal cord are affected.
- ❖ Symptoms develop over weeks. (Not sudden onset)
- ❖ Early clinical signs:

1. Mild ataxia.
2. lower-extremity numbness and tingling.(bilateral).
3. Can progress to spastic weakness of the lower extremities.
4. Complete paraplegia (poor outcome despite Tx).

B. Metabolic disorders:

-Hypoglycemia:

- ➢ Effect 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
- ➢ The Tx is giving glucose immediately

-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. (Because liver responsible for metabolism of ammonia so it rise in those people)
- Early stages: flapping tremor “asterixis”.
- Elevated levels of ammonia, inflammation and hyponatremia.
- Ammonia metabolism occurs only in astrocytes “glutamine synthetase” .
- The microscopic feature for hepatic Encephalopathy is (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) and they present with:
  1. Truncal ataxia
  2. Unsteady gait
  3. Nystagmus.