CNS

Doctor 202

Pathology

Modified ( )

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Neurodegenerative disorders-3

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Different diseases

Based on the site/ structure that is affected in the brain :

- **Involving the hippocampus and cortex**>>>> cognitive changes (memory disturbances, behavior and language) >>>> 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)

This lecture topics:

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

  The cerebellum is responsible for coordination

- **Involving the motor system** >>> difficulty swallowing and respiration with muscle weakness >> (AMYOTROPHIC LATERAL SCLEROSIS)

  Starting from the higher motor neurons in the brain stem and cortex for the cranial nerves, and the lower motor neurons in the anterior horn of the spinal cord and the nerves reaching the muscle (collectively produce muscle weakness

Spinocerebellar Ataxias SCA

Sensory ataxia: lose of coordination due to losing the sensory input.

- **Heterogeneous group of diseases**, characterized by cerebellar and sensory ataxia, spasticity, and sensorimotor peripheral neuropathy. → Muscle weakness and tingling sensation
- 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.

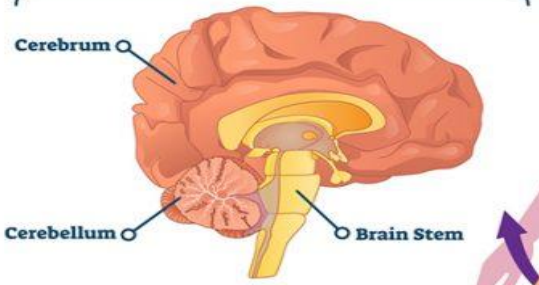
If the cerebellum is affected, we are talking about ataxia
If the spinal cord is affected, we are talking about spasticity
If the peripheral nerves are affected, we are talking about peripheral neuropathy

ATAXIA

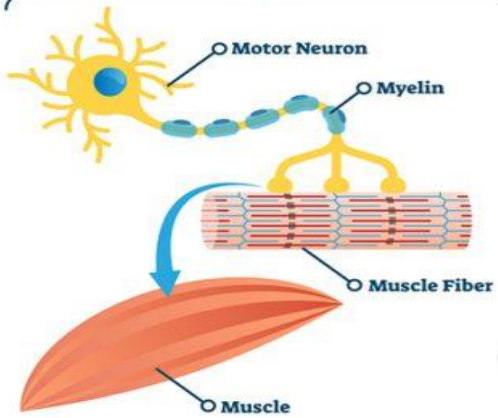
Ataxia is a Degenerative Disease of the Nervous System Consisting of Lack of Voluntary Coordination of Muscle Movements

ATAXIA is a Clinical Manifestation Indicating DYSFUNCTION of the Parts of The NERVOUS SYSTEM that COORDINATE MOVEMENT

Brain



Neuromuscular Junction



ATAXIA SYMPTOMS

Lack of Coordination

Eye Movement Abnormalities

Slurred Speech

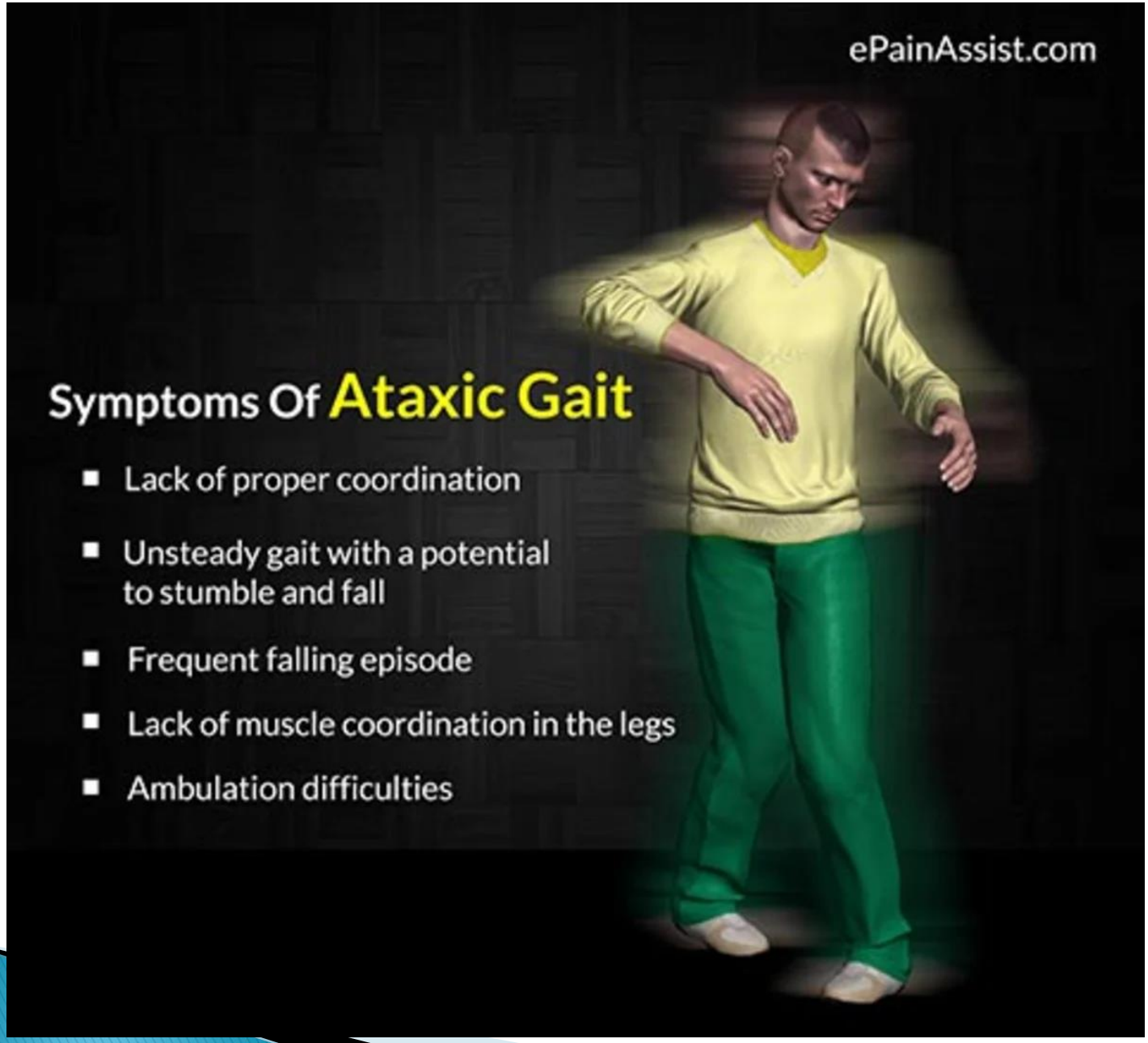
Trouble Eating and Swallowing

Heart Problems

Tremors and Deterioration of Fine Motor Skills

Gait Abnormalities

Difficulty Walking and Poor Balance


ePainAssist.com
Symptoms Of Ataxic Gait
Lack of proper coordination
Unsteady gait with a potential to stumble and fall
Frequent falling episode
Lack of muscle coordination in the legs
Ambulation difficulties

DIAGNOSTIC TESTS

FINGER to NOSE TEST

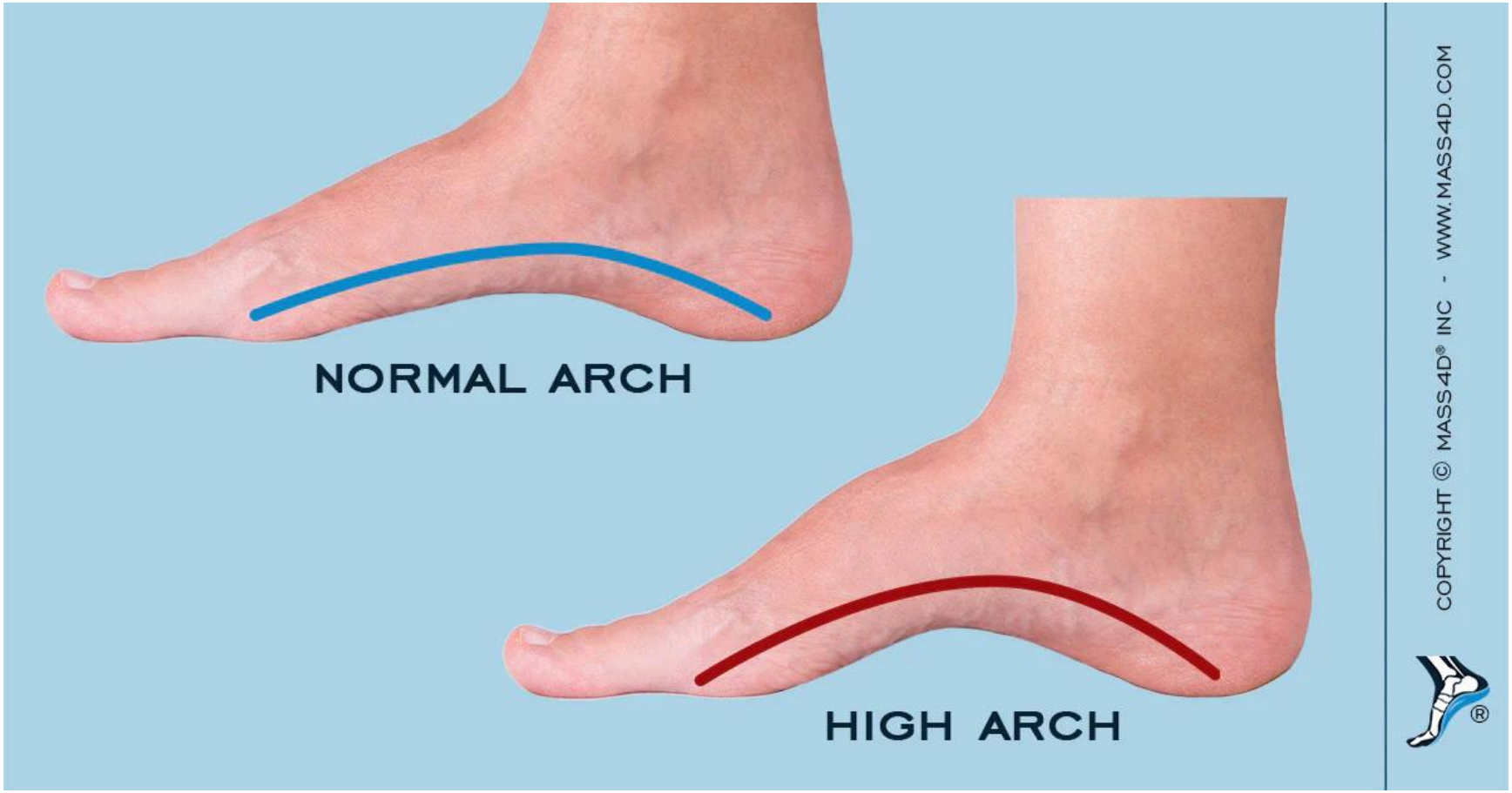
HEEL to SHIN TEST

The patient hand will start moving left & right due to losing coordination

Friedreich ataxia

- Most important SCA.
- Autosomal recessive disorder.
- First decade of life. Children
- Gait ataxia, followed by hand clumsiness and dysarthria. They even have a problem with the articulation of speech
- Pes cavus and kyphoscoliosis.
- High incidence of cardiac disease and diabetes.

Pes cavus



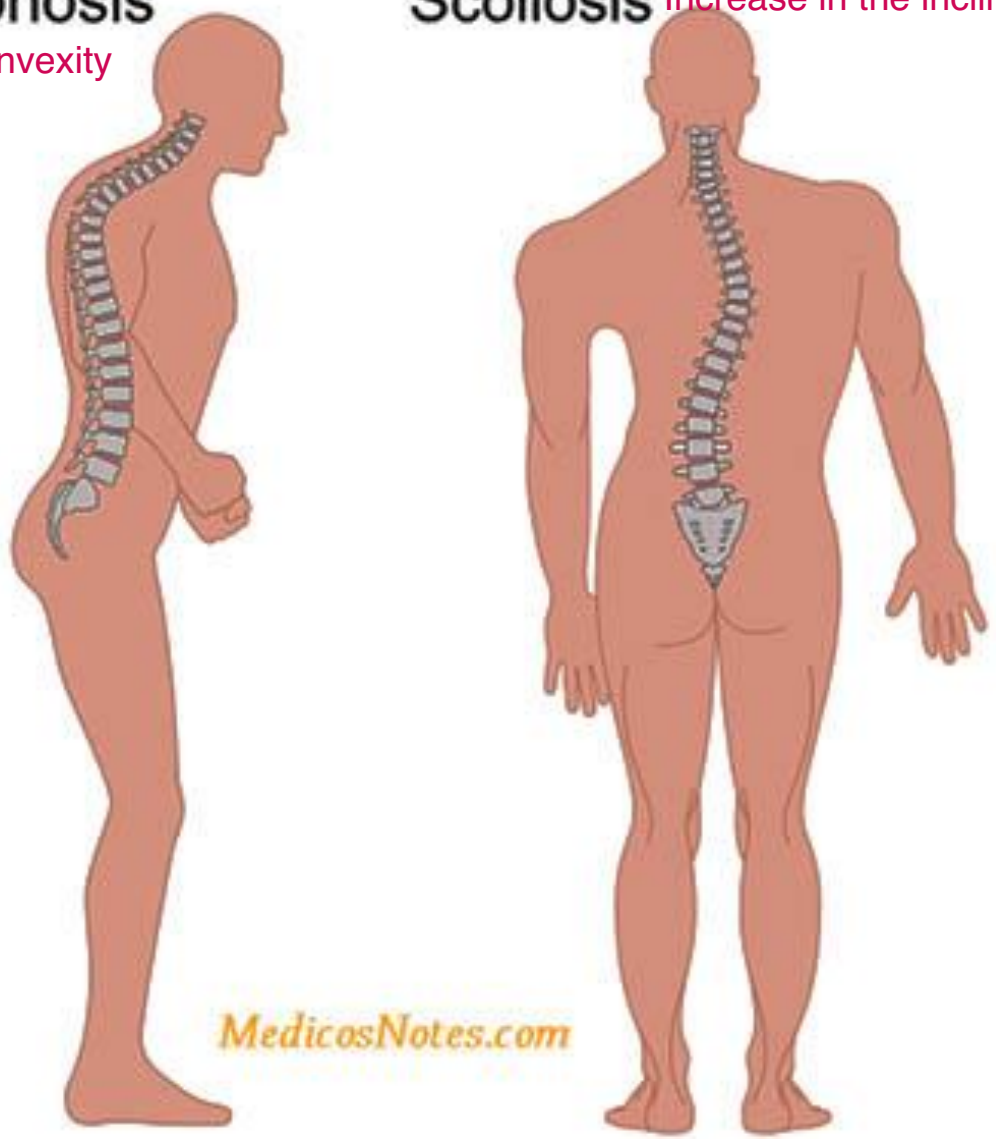
Abnormal Spine

Kyphosis

Increase in the convexity

Scoliosis

Increase in the inclination/deviation



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)

So it controls the oxygen reduction reaction in the mitochondria to produce the ATP

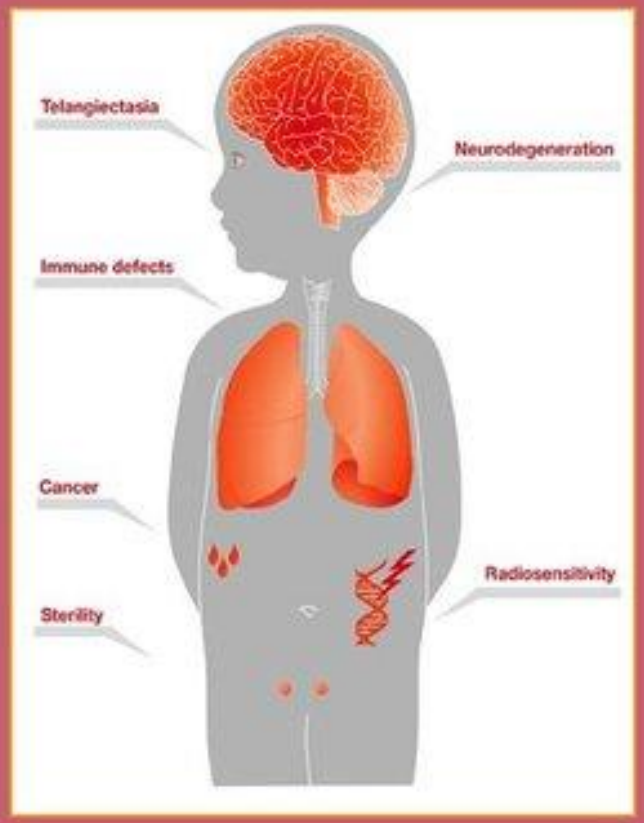
Unlike the other neurodegenerative diseases, as Alzheimer.

It's an inherited disease, patients have a mutation, they are genetically unstable, the genome is exposed to have a recurrent mutation, so malignancy is a risk factor.

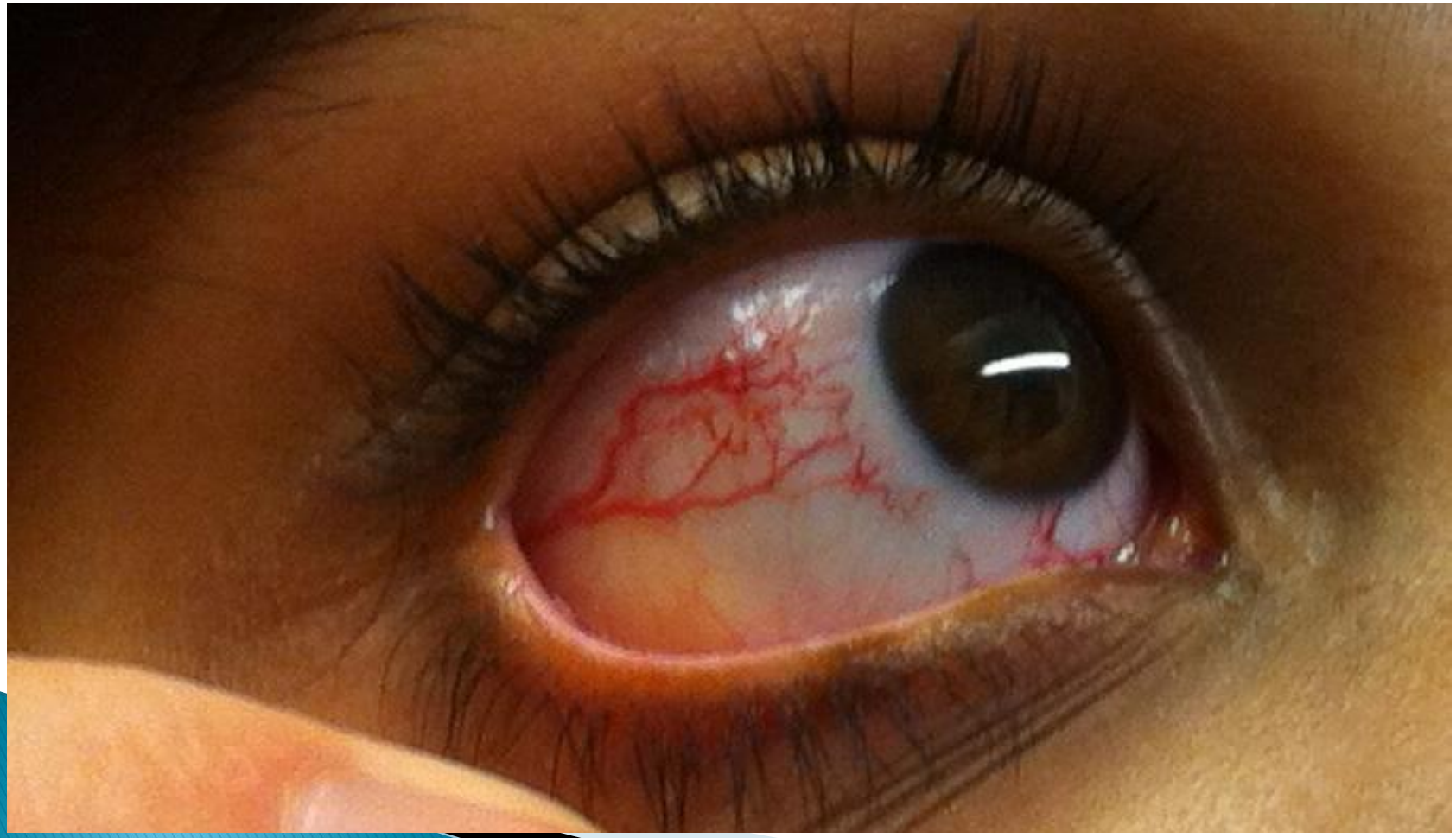
Ataxia Telangiectasia

Characterized by:

- Cerebellar deterioration
- Oculocutaneous telangiectasia
- Immunodeficiency
- Genomic Instability
- Acute sensitivity to ionizing radiation
- Predisposition to malignancy

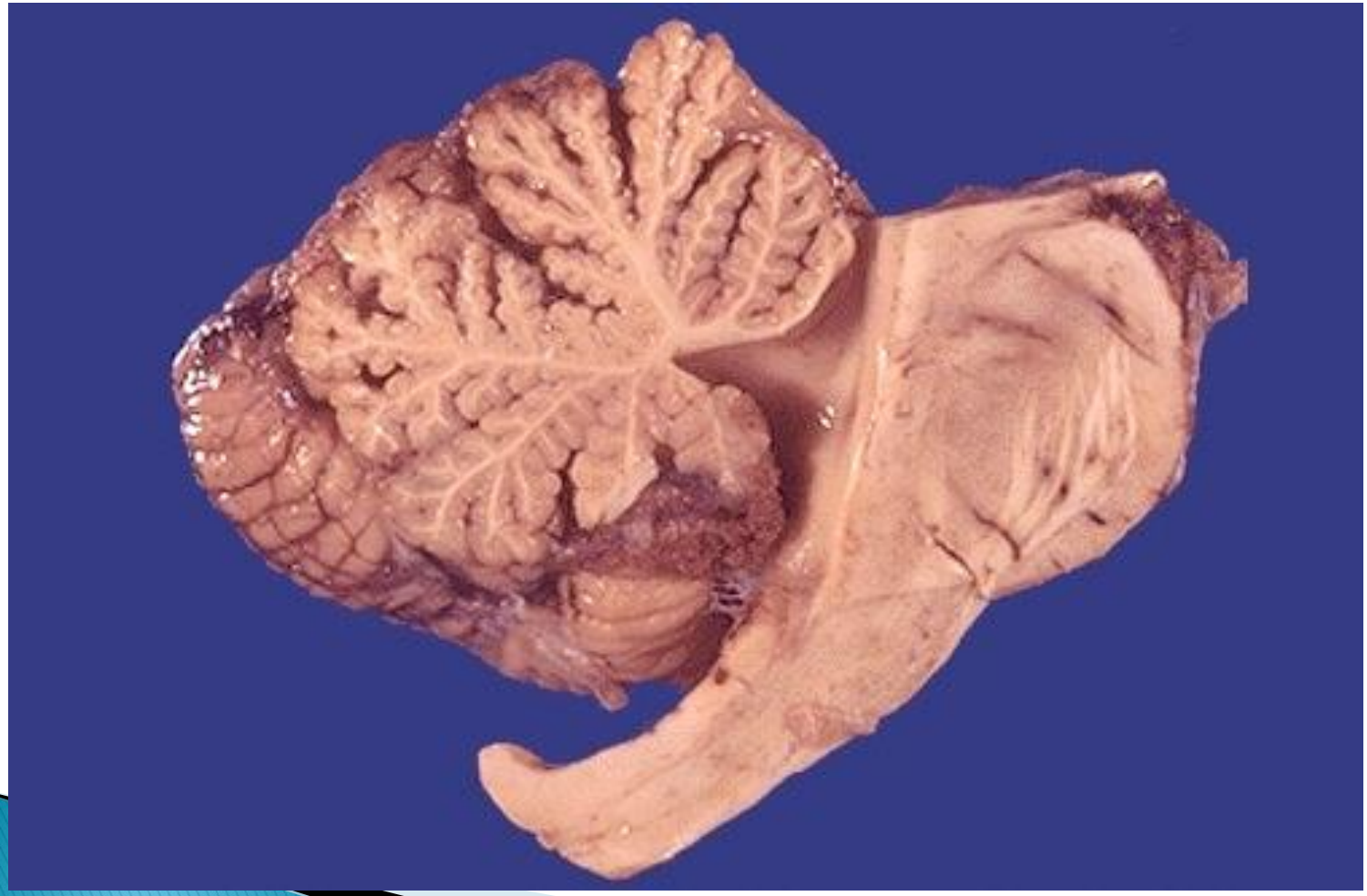


Telangectasia



Cerebellar atrophy

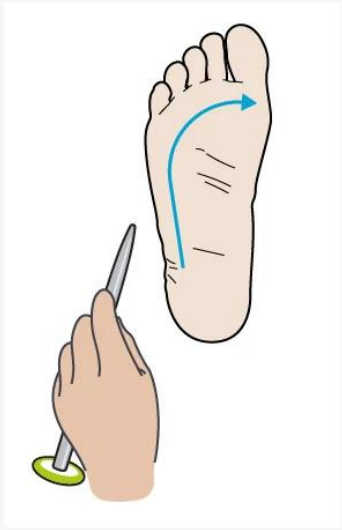
One of the macroscopic morphology changes due to neurons degeneration



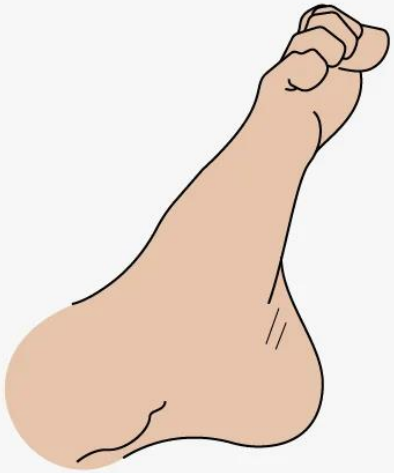
Amyotrophic Lateral Sclerosis

- 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. Contraction and twitching with the muscles
- **Loss of upper motor neurons** results in paresis, hyperreflexia, spasticity, along with a Babinski sign.

The Babinski Reflex

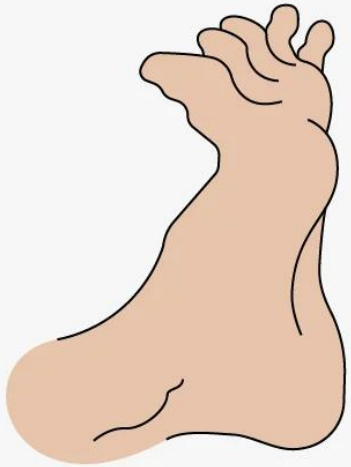


test



negative

Normal



positive

Abnormal

MedicalNewsToday

- 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.
- 5^{th} decade and after.

Pathogenesis

- Most cases are sporadic.
- 10% are familial (AD, early onset) autosomal dominant
- Mutations in the superoxide dismutase gene, *SOD1,* on chromosome 21. This gene is responsible for removing the free radicals
- Generate abnormal misfolded protein >>> trigger the unfolded protein response >>>> apoptotic death of neurons. The pathogenesis of the disease:

- **OTHER MUTATIONS:** Don't worry about them they're not required for the exam purposes
- 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 (f*asciculations)*
- 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.

A subtype of amyotrophic lateral sclerosis

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

Remember, bulbar nerves are the cranial nerves.

MORPHOLOGY

- **MACROSCOPY:**

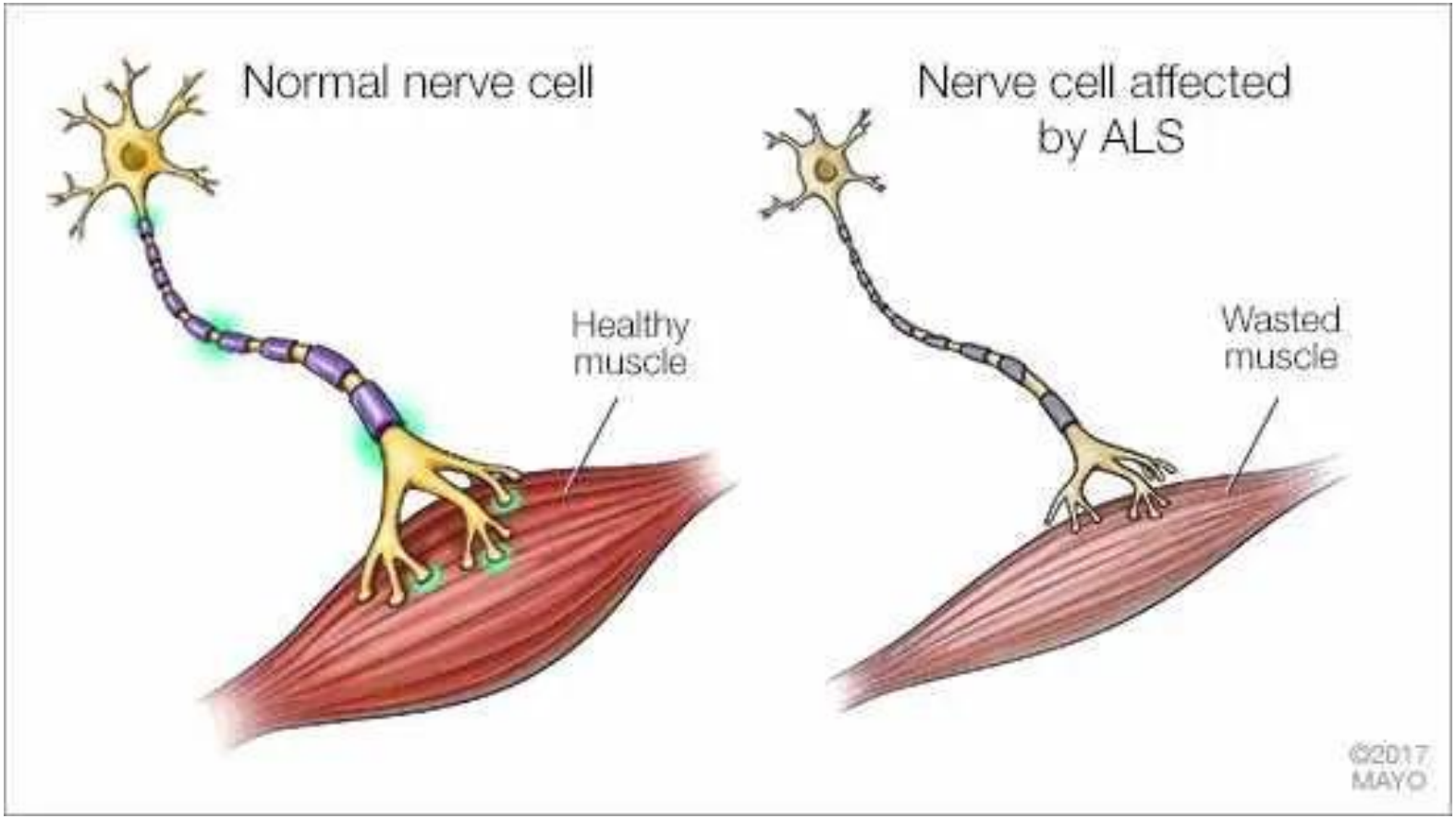
Because we have a lose in the anterior horn of the spinal cord, so so the nerves goes through it are atrophied

- 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

Due to the lose of neurogenic activation.


Normal nerve cell
Healthy muscle
Nerve cell affected by ALS
Wasted muscle
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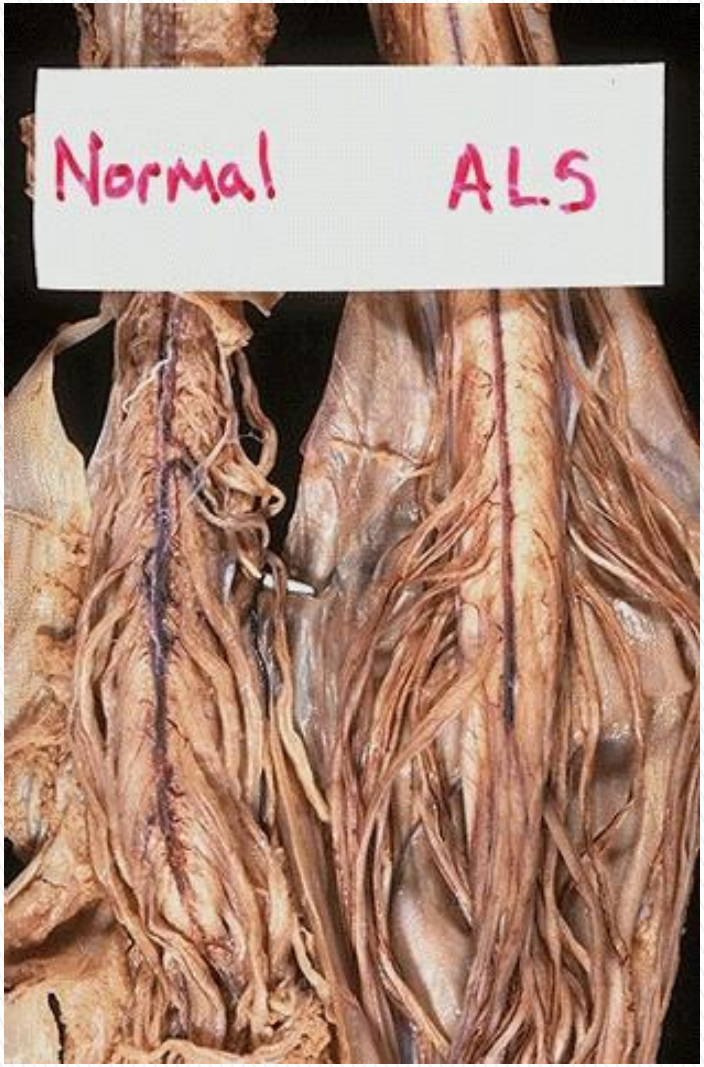
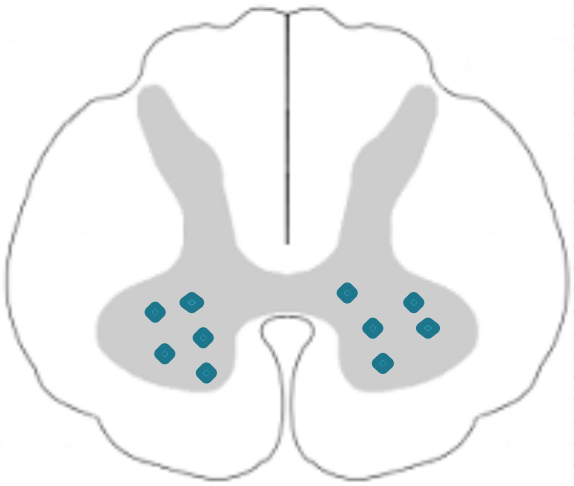
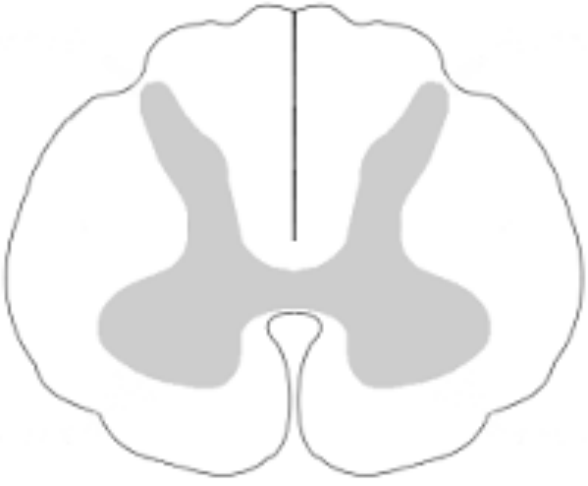


- Loss of anterior horn cells>> (ventral) spinal motor nerve roots demonstrate **atrophy**, as seen here in comparison with **normal** ventral spinal cord nerve roots.

Normal versus ALS



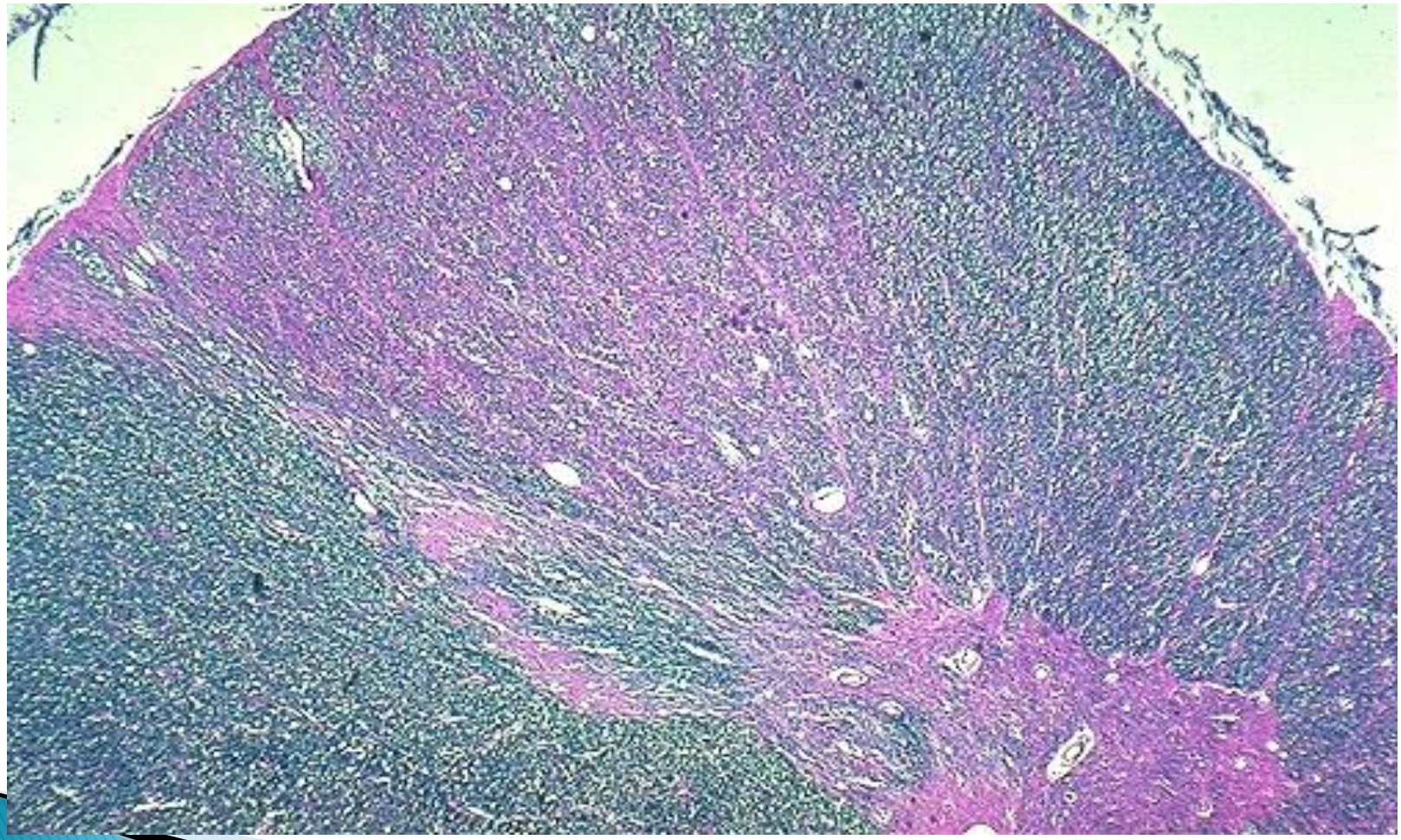
Lower motor neurons



They are lost

Lateral column degeneration with gliosis--the "sclerosis" of ALS.

Pink central area



Important

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

ACQUIRED METABOLIC AND TOXIC DISTURBANCES

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

Highly active and the energy source for this activities is the glucose,
So hypoxia and hypoglycemia affected largely on the brain tissues.

Nutritional Diseases

- **Thiamine Deficiency**:
- Chronic alcoholism, gastric disorders, gastric bypass surgery, or persistent vomiting.

- **Beriberi (systemic manifestations)**
- **Wernicke encephalopathy** Neurologic manifestation
- Abrupt onset of confusion
- Ataxia.
- Abnormalities in eye movement

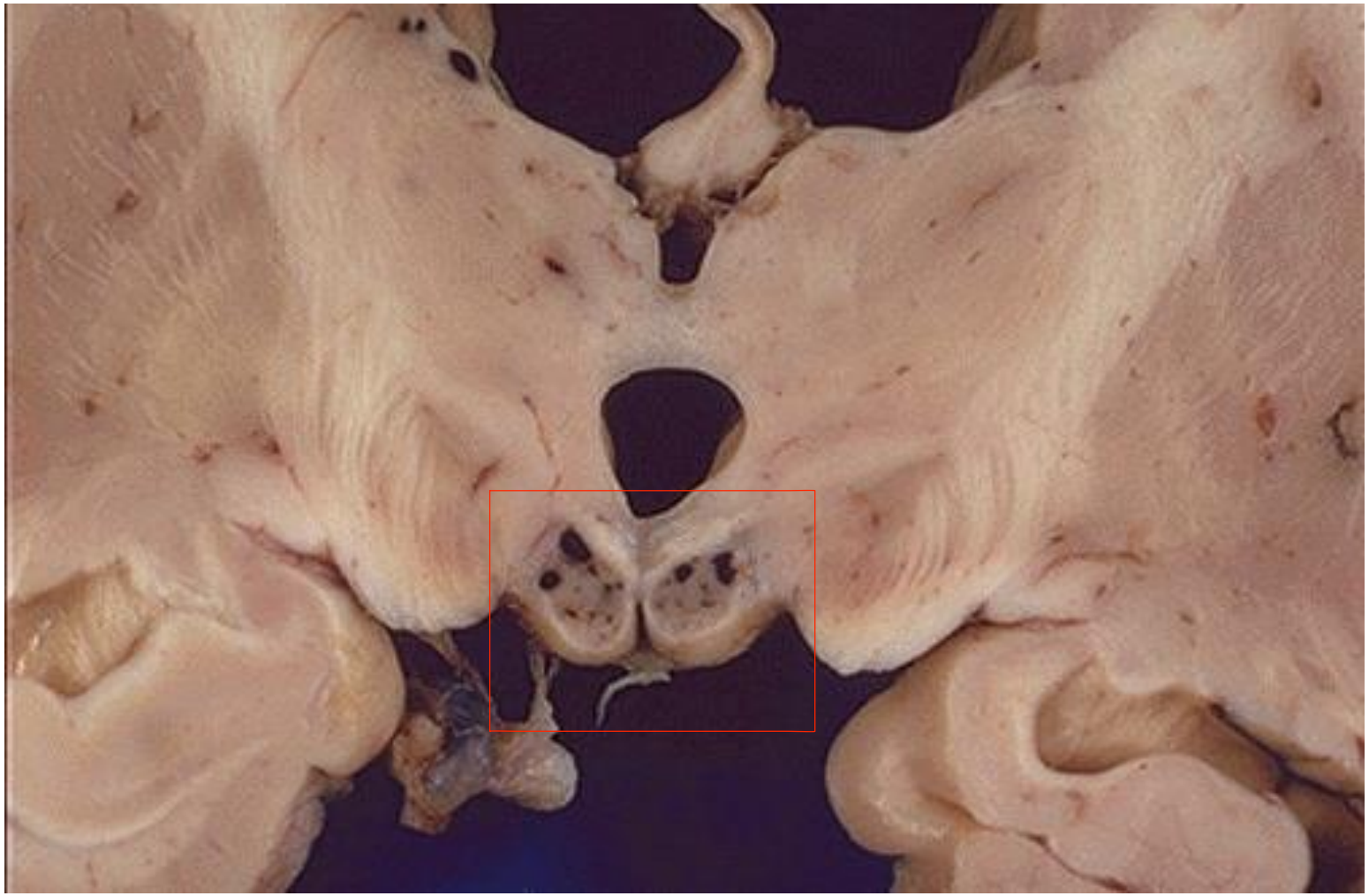
- **Tx:** thiamine reverses deficits.
- **Delayed Tx**: irreversible profound memory disturbance (Korsakoff syndrome)

- ***Wernicke-Korsakoff syndrome***

MORPHOLOGY

The most important feature

- 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. Gradual manifestation of symptoms
- Early clinical signs:

1. Mild ataxia.
2. lower-extremity numbness and tingling.
3. Can progress to spastic weakness of the lower extremities
4. Complete paraplegia (poor outcome despite Tx) Due to delayed treatment And it's unfortunately irreversible.

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.

So sometimes hypoglycemia are more dangerous than hyperglycemia to the brain tissues.

- **Hyperglycemia**

- Uncontrolled diabetes mellitus.
- Ketoacidosis or hyperosmolar coma.
- Confusion, stupor, and eventually coma.
- Intracellular dehydration.
- Rapid correction can produce severe cerebral edema (correct gradually). So it should be a slow or a gradual correction.

- **Hepatic Encephalopathy:**

- Hepatic dysfunction leads to depressed levels of consciousness or coma. In patients with hepatic diseases like cirrhosis or hepatic failure.
- Early stages: flapping tremor "asterixis".
- Cause:
- Elevated levels of ammonia, inflammation and hyponatremia.
- Ammonia metabolism occurs only in astrocytes "glutamine synthetase" .
- They have not association with Alzheimer disease.
- (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) : Less symptoms but

1. Truncal ataxia
2. Unsteady gait
3. Nystagmus.

Also, they have a thiamine deficiency, so it could be a combined disease


اللهم كن لأهل
فلسطين نصيرًا وظهيرًا
اللهم ارحم شهداءهم، وداوِ
جرحاهم، واحقن دماءهم