MID

Lecture 6

Pathology Mind Maps

Neurodegenerative Disorders - 3

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This file contains the lecture material presented through mind maps to make the information clearer, more organized, and easier to follow. It is designed to simplify studying and make revision more effective.

We truly hope you find it beneficial.
If it helps you in any way, please remember us in your prayers.

Best of luck in your studies💙!

(1) Spinocerebellar Ataxias

Involving the **cerebellum** → ataxia
1- SPINOCEREBELLAR ATAXIA
2- FRIEDRICH ATAXIA
3- ATAXIA TELANGECTASIA)

Spinocerebellar degeneration - General charactertics :

- 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.**

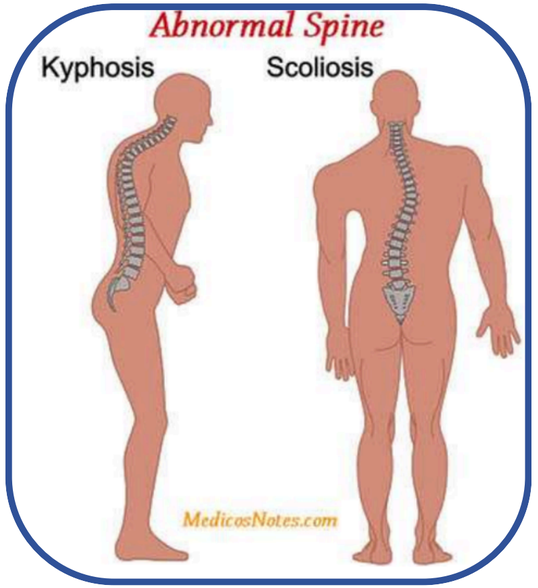
Definition:

- 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.**

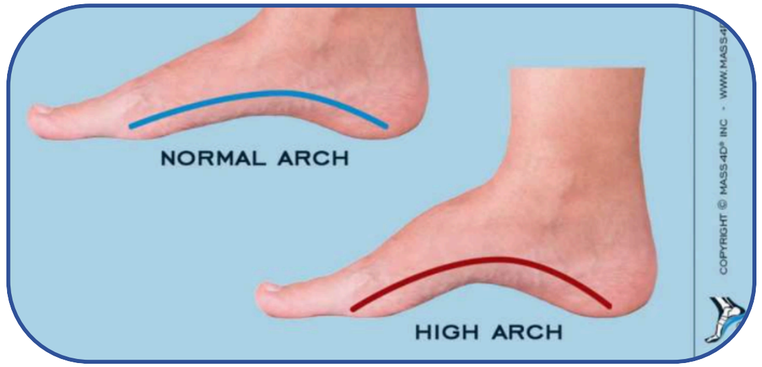
(2) Friedreich ataxia

General charactertics :

- **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 <u>limited</u> to **40 or 50** years of age.



kyphoscoliosis



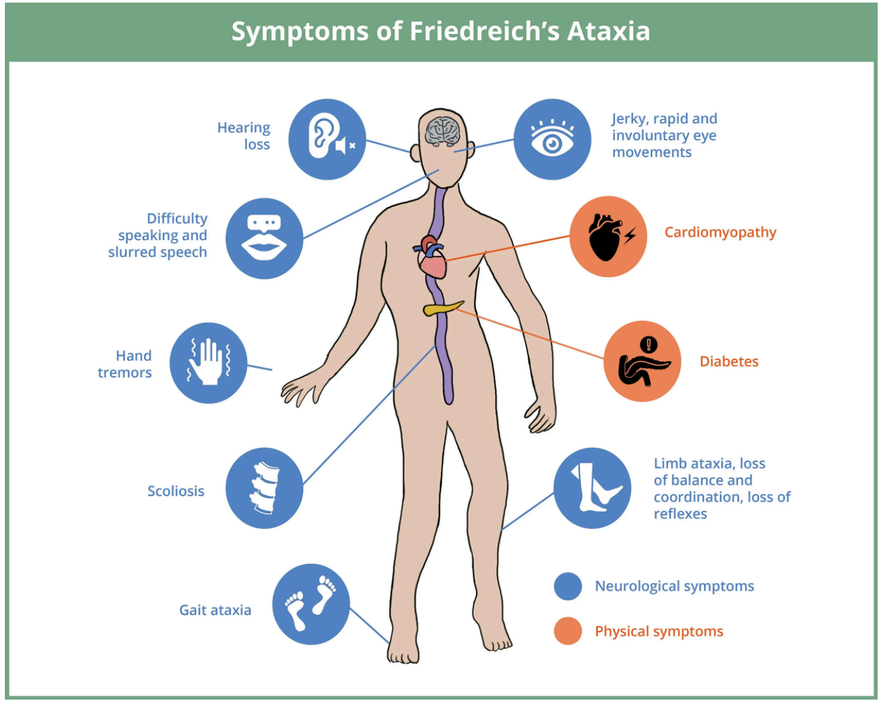
Pes cavus

Mutations :

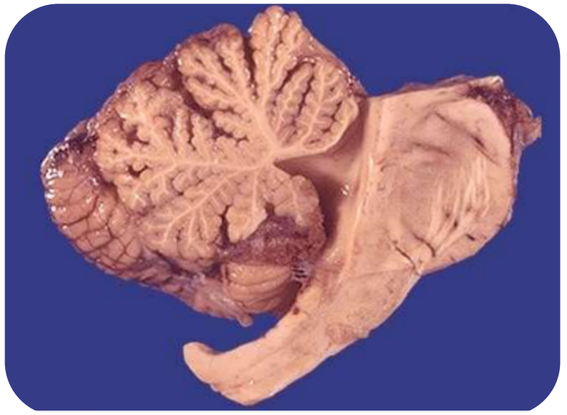
- Caused by **GAA** trinucleotide repeat expansion.
- In the gene encoding **Frataxin** protein (regulates mitochondrial iron).
- Repeat expansion >> transcriptional silencing>> decreased frataxin>>mitochondrial dysfunction>>oxidative damage (ROS).
- The damage is <u>not</u> caused by the protein deposition. (**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.**



(3) Ataxia telangectasia



Cerebellar atrophy

General charactertics :

- **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

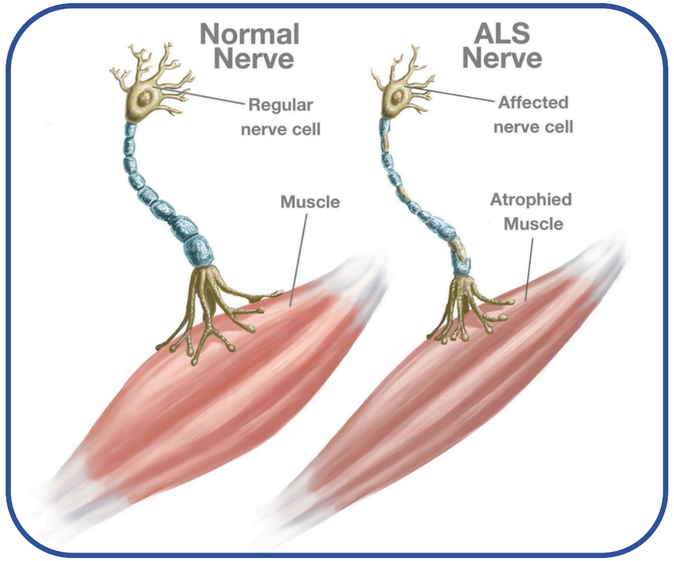
Telangiectasia

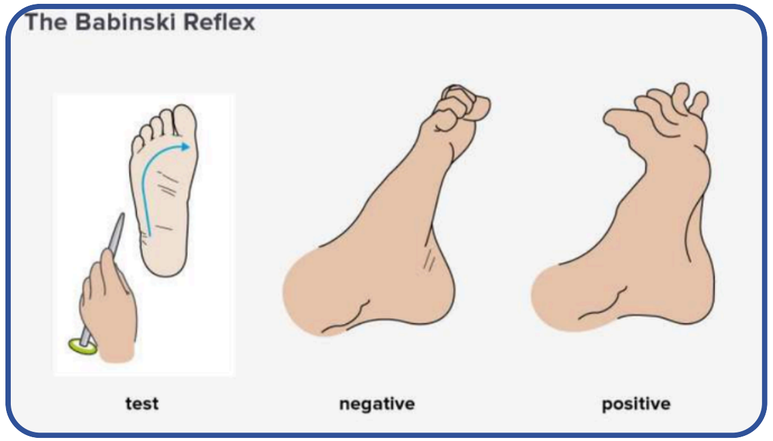
(1) Amyotrophic Lateral Sclerosis

Involving the **motor** system → difficulty swallowing and respiration with muscle weakness.
1-Amyotrophic lateral sclerosis,
2-Spinal muscular atrophy

General charactertics :

- 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.
- **5 th** 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**.

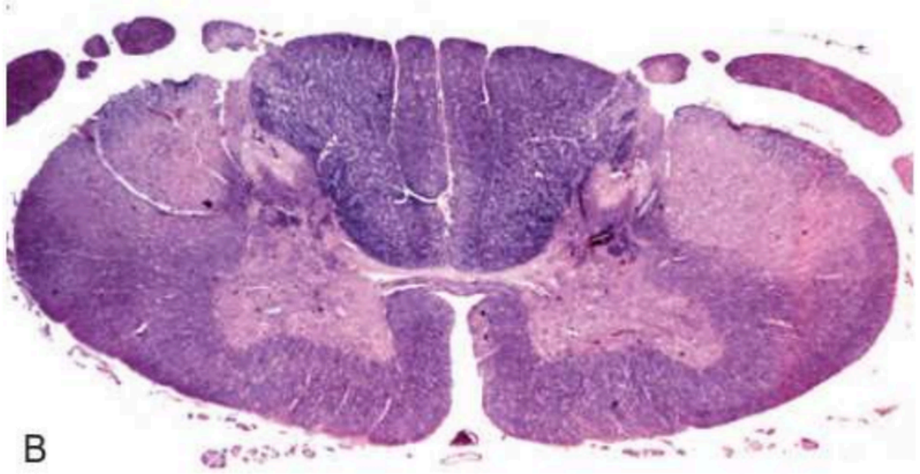
Morphology - MACROSCOPY :

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

Morphology - 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

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.

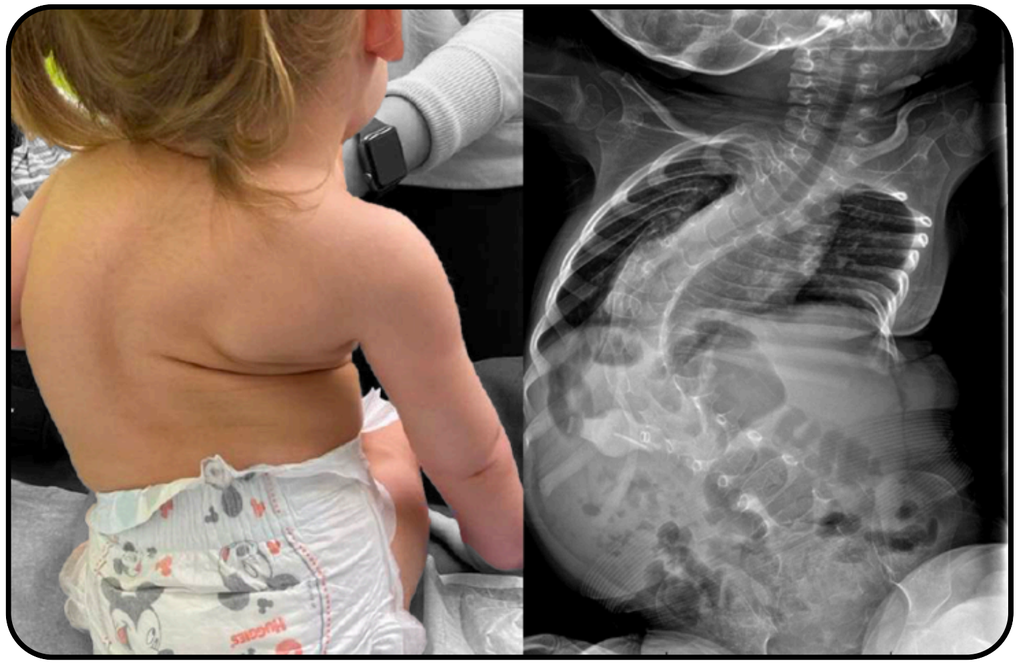
(2) Spinal muscular atrophy (SMA)

General charactertics :

- 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



اللهم اجعل أجر هذا العمل صدقة جارية عن روح **عمر عطيه عوده المرابي**

- اللَّهُمَّ اغْفِرْ له وَارْحَمْهُ، وَاعْفُ عنْه وَعَافِهِ، وَأَكْرِمْ نُزُلَهُ، وَوَسِّعْ مُدْخَلَهُ، وَ اغْسِلْهُ بمَاءٍ وَثَلْجٍ وَبَرَدٍ، وَنَقِهِ مِنَ الخَطَايَا كما يُنَقّى الثَّوْبُ الأبْيَضُ مِنَ الدَّنَسِ.
- اللَّهُمَّ أبدله داراً خيراً من داره، وأهلاً خيراً من أهله، وأدخله الجنّة، وأعذه من عذاب القبر ومن عذاب النّار.
- اللهمّ يمّن كتابه، ويسّر حسابه، وثقل بالحسنات ميزانه، وثبّت على الصراط أقدامه، وأسكنه في أعلى الجنات، بجوار حبيبك محمد صلّى الله عليه وسلم.
- اللهم اغفر لحينا وميتنا وشاهدنا وغائبنا وصغيرنا وكبيرنا وذكرِنا وأنثانا اللهم من أحييته منا فأحيِه على الإسلام ومن توفيته منا فتوفه على الإيمان اللهم لا تحرمنا أجره ولا تضلنا بعده.
- اللهم اغفر له وارفع درجته في المهديين، واخلفه في عقبه في الغابرين، واغفر لنا وله يا رب العالمين، وافسح له في قبره، ونوّر له فيه.
- اللَّهُمَّ أنزل على أهله الصّبر والسلوان وارضهم بقضائك.

اللهم لا تفجعنا بأنفسنا ولا أهلنا ولا أحبتنا، اللهم أعوذ بك من فواجع الأقدار ومن مصائب الدنيا وتقلب حوادثها، اللهم إنا نخاف الفقد فلا تحملنا ما لا طاقة لنا به.