# Neurodegenerative Diseases (3)

## Neurodegenerative diseases according to the location:

1. Diseases involving the **hippocampus** and **cortex** >>>> cognitive changes (memory disturbances, behavior and language) >>>> dementia >>>>> Alzheimer Disease (AD), Frontotemporal Dementia (FTD), Pick Disease (subtype of FTD)

2. Diseases involving the **basal ganglia** >>>>> movement disorders >>>> hypokinesia (Parkinson Disease) OR hyperkinesia (Huntington Disease)

3. Diseases involving the **cerebellum** >>>> ataxia >>> (Spinocerebellar Ataxia, Friedrich Ataxia, Ataxia Telangiectasia)

4. Diseases involving the **motor system** >>> difficulty swallowing and respiration with muscle weakness >> (Amyotrophic Lateral Sclerosis)

## Disease involving the cerebellum

## Ataxia

(NOTE: Ataxia is not a specific disease, rather it is a set of symptoms describes more than one disease)

### - Definition:

Ataxia is a clinical manifestation indicating dysfunction of the CNS parts that coordinate movement.

### - Symptoms:

- Lack Of Coordination
- Eye Movement Abnormalities (Nystagmus)
- Slurred Speech
- Trouble Eating and Swallowing
- Heart Problems
- Tremors and deterioration of fine Motor Skills
- Gait Abnormalities
- Difficulty Walking and Poor Balance

### - How to diagnose Ataxia?

- Finger to Nose Test
- Heel to Shin Test

## 1st Spinocerebellar Ataxias

- Heterogeneous group of diseases, differ in causative mutations, patterns of inheritance, age at onset, and signs and symptoms.

- Characterized by cerebellar and sensory ataxia, spasticity, and sensorimotor peripheral neuropathy.

- Affects **cerebellar cortex**, spinal cord, other brain regions, and peripheral nerves variably.

- Several forms of SCAs are caused by **CAG repeat expansions** (like HD), causing intranuclear inclusions, among other mutations.

## A. Friedrich Ataxia

- Most important SCA.

- Autosomal recessive disorder.

- First decade of life.

### - Symptoms:

- Gait ataxia, followed by hand clumsiness and dysarthria
- Pes cavus (high arched foot)
- kyphoscoliosis
- High incidence of cardiac disease and diabetes

### - Mutations:

**GAA trinucleotide repeat expansion in Frataxin protein gene**.

### - Pathogenesis:

- Frataxin protein (regulates mitochondrial iron).

- GAA trinucleotide repeat expansion in Frataxin protein gene >> transcriptional silencing >> decreased frataxin >> mitochondrial dysfunction >> oxidative damage (due to increase in ROS).

- The damage is not caused by the protein deposition (like other neurodegenerative diseases). (It is caused due to loss of Frataxin protein)

## 2nd Ataxia Telangiectasia

- Inherited disease, characterized by:

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

# Disease involving the motor system

## 1st 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)**

- Sensation usually is unaffected, but cognitive impairment is not infrequent.

- Male predominance.

- 5th decade and after.

- Most cases are **Sporadic**, 10% are familial (Autosomal Dominant, early onset).

- Pathogenesis:

-There are many mutations that cause ALS, most important one is:

(1) **Mutation in the superoxide dismutase gene, SOD1, on chromosome 21**.

Generate abnormal misfolded protein >>> trigger the unfolded protein response >>>> apoptotic death of neurons.

- Other Mutations (less important):

(2) Hexanucleotide repeat expansion of C9orf72 (familial forms)
(3) **TDP43** (also associated with FTLD (Frontotemporal Lobe Dementia))
(4) FUS gene

- There is genetic and clinical overlap Between ALS and FTLD.

- Symptoms:

- Begins with subtle asymmetric distal extremity weakness.
- As the disease progresses, muscle strength and bulk diminish (Muscular Atrophy).
- 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 (patients can have disease in one of them, not both).

## A. Bulbar Amyotrophic Lateral Sclerosis

- Degeneration of the lower brain stem's cranial motor nuclei.

- There are abnormalities of swallowing and speaking.

- Morphology:

- Macroscopically:

1. Anterior Horn of the spinal cord is thin and gray.
2. In severe cases: atrophy of precentral gyrus (motor cortex).

- Microscopically:

1. Reactive gliosis and loss of anterior horn neurons (throughout the spinal cord).
2. Cytoplasmic inclusions that contain TDP43.
3. Skeletal muscles show neurogenic atrophy.

- In case of Bulbar Amyotrophic Lateral Sclerosis:

1. Similar changes in motor cranial nerve nuclei.
2. Sparing of those supplying the extraocular muscles.

The End of The Neurodegenerative Diseases Topic

# Acquired Metabolic and Toxic Disturbances

- Common causes of neurologic illnesses.

- Because of its high metabolic demands, the brain is particularly vulnerable to **nutritional diseases**, alterations in metabolic state (**metabolic disorders**) and **Toxins**.

## Nutritional Diseases

### 1st Thiamine Deficiency

- Causes:

- Chronic alcoholism
- Gastric disorders or gastric bypass surgery
- Persistent vomiting

- Symptoms:

1. **Beriberi** (Systemic manifestations)
2. **Wernicke encephalopathy** (Neurologic manifestations)
   - Abrupt onset of confusion
   - Ataxia
   - Abnormalities in eye movement

- Treatment (Tx): Thiamine Supplement

- Delayed Tx: irreversible profound memory disturbance (**Korsakoff syndrome**)

→ **Wernicke-Korsakoff syndrome** (The symptoms of Thiamine deficiency + Delayed Tx)

- Morphology:

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

### 2nd 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.

- Can progress to:

  - Spastic weakness of the lower extremities.
  - Complete paraplegia (poor outcome despite Tx).

# Metabolic Disorders

## 1st Hypoglycemia

- Effect resembles those of global hypoxia (anoxia).

- **Hippocampal neurons** are particularly susceptible.

- Cerebellar Purkinje cells are relatively spared.

- If level and duration of hypoglycemia are sufficiently severe >> widespread injury.

## 2nd Hyperglycemia

- Caused by uncontrolled diabetes mellitus.

- Hyperglycemic state can be associated with ketoacidosis or hyperosmolar coma.

- Patients develop confusion, stupor, and eventually coma due to dehydration of neuronal cells.

- Rapid correction can produce severe cerebral edema (correct gradually).

## 3rd Hepatic Encephalopathy

- Decreased hepatic function leads to depressed levels of consciousness or coma.

- In early stages: flapping tremor (Asterixis).

- Elevated levels of ammonia which liver normally clears, inflammation and hyponatremia cause the changes in brain function.

- Pathogenesis:

  - In the CNS, ammonia metabolism occurs only in astrocytes by **glutamine synthetase**.

  - Liver dysfunction >> elevated ammonia >> astrocytes in the cortex and basal ganglia develop swollen pale nuclei (due to increase in function).

  - **Alzheimer type II cells**: astrocytes in the cortex and basal ganglia with swollen pale nuclei. (No relation between Alzheimer type 2 cells and Alzheimer Disease, it is just a name)

# Toxic Disorders

## 1st Ethanol

**Acute intoxication** is reversible.

- Excessive intake leads to profound metabolic disturbances (brain swelling and death).

**Chronic alcoholism**: in 1% of cases, cerebellar dysfunction (due to atrophy in the anterior vermis)

- Symptoms of cerebellar dysfunction (due to atrophy in the anterior vermis)

- Truncal ataxia
- Unsteady gait
- Nystagmus

Done By: Yahya Mohammed and Tareq Hajeer

# Summary

## Ataxia

- Definition: Clinical sign indicating CNS dysfunction affecting movement coordination.
- Symptoms: Lack of coordination, nystagmus, slurred speech, swallowing difficulties, tremors, gait abnormalities.

## Spinocerebellar Ataxias (SCAs)

- Features: Heterogeneous group with various genetic mutations, inheritance patterns, and onset ages.
- Common Symptoms: Cerebellar and sensory ataxia, spasticity, peripheral neuropathy.
- Caused by many mutations, most important one is **CAG repeat expansions** (like HD), causing intranuclear inclusions, among other mutations.
- The most important SCA is **Friedreich Ataxia.**

## Friedreich Ataxia

- Autosomal recessive disorder with onset in childhood, characterized by gait ataxia, hand clumsiness, pes cavus (high arched foot), and kyphoscoliosis.
- Caused by **GAA trinucleotide repeat expansion in Frataxin protein gene**.
- The damage is not caused by the protein deposition (like other neurodegenerative diseases). (It is caused due to loss of Frataxin protein).

## Ataxia Telangiectasia

- Characteristics: Inherited disorder with cerebellar deterioration, immunodeficiency, and predisposition to malignancy.

## Amyotrophic Lateral Sclerosis (ALS)

- Pathophysiology: Death of lower and upper motor neurons, leading to UMNL and LMNL symptoms.
- Genetics: Caused by mutations in various genes, most important one is SOD1, leading to misfolded proteins and neuronal death. TDP43 mutation also cause ALS (like FTLD)
- Clinical Presentation: Asymmetric distal extremity weakness and atrophy. May progress to involve respiratory muscle (the usual cause of death). Bulbar symptoms (swallowing, speech) if disease affect the cranial nerves nuclei.

# Summary

## Nutritional Diseases

### Thiamine Deficiency

- Causes: Chronic alcoholism, gastric disorders, persistent vomiting.
- Symptoms: Beriberi (systemic manifestations), Wernicke encephalopathy (neurologic manifestations).
- Treatment: Thiamine supplement; delayed treatment can lead to irreversible memory disturbance (Korsakoff syndrome).
- Morphology: Hemorrhage and necrosis foci, cystic spaces in mammillary bodies and adjacent areas.

### Vitamin B12 Deficiency

- Causes anemia and neurologic deficits.
- Leads to subacute combined degeneration of the spinal cord.

## Metabolic Disorders

### Hypoglycemia

- Hippocampal neurons are particularly vulnerable.
- Prolonged and severe hypoglycemia can cause widespread neuronal injury.

### Hyperglycemia

- Associated with uncontrolled diabetes mellitus.
- Can lead to confusion, stupor, and coma due to neuronal dehydration.
- Rapid correction may result in cerebral edema; correct gradually.

### Hepatic Encephalopathy

- Decreased hepatic function leads to depressed consciousness.
- Early signs include flapping tremor (asterixis) and elevated ammonia levels.
- Pathogenesis: Liver dysfunction >> elevated ammonia >> astrocytes in the cortex and basal ganglia develop swollen pale nuclei (Alzheimer Type 2 cells).

## Toxic Disorders

### Ethanol

- Acute intoxication is reversible; excessive intake can lead to brain swelling and death.
- Chronic alcoholism may cause cerebellar dysfunction.