ATAXIA

SYMPTOMS:

➢Lack Of Coordinations ➢Eye Movement Abnormalities(Nystagmus)

➢Gait Abnormalities ➢Slurred Speech ➢Heart Problems

➢Tremors and deterioration of fine motor skills

➢Difficulty Walking And Poor Balance ➢Trouble Eating And Swallowing

Spinocerebellar Ataxias(SCA)

• Heterogeneous group of diseases, characterized by cerebellar ataxia and sensory ataxia, spasticity, and sensorimotor peripheral neuropathy.

• DIFFER in causative mutations, patterns of inheritance, age at onset, and signs and symptoms.

• Several forms of SCA are caused by CAG repeat expansions(like HD).

1) Cerebellar ataxia: disrupts the part of the brain that manages how different parts of your brain work together.

2) Sensory ataxia: disrupts your self positioning sense, which lets your brain track where each body part is in space…The patients get worse if they close their eyes.

3) Vestibular ataxia: disrupts your sense of balance.

Diagnostic Tests: ➢ Finger to nose test. ➢ Heel to shin test.

Friedreich Ataxia

• Most important SCA. • Autosomal recessive disorder.

Symptoms :

• Gait Ataxia, followed by Hand Clumsiness and Dysarthria.

• High incidence of Cardiac disease and Diabetes.

• Pes Cavus(High Arched Foot) and Kyphoscoliosis.

Mutations :

• GAA trinucleotide repeat expansion. The gene codes for Frataxin Protein which regulates mitochondrial iron. Is decreased by Transcriptional Silencing leading to mitochondrial dysfunction and oxidative damage(ROS).

<< The damage is NOT caused by the protein deposition>>

Ataxia Telangiectasia

Characterized by :

• Cerebellar deterioration>>> cerebellar atrophy>>> atrophied Gyri & dilated Sulci

• Oculocutaneous telangiectasia (Telangiectasia = dilated tortuous capillaries).

• Immunodeficiency . • Genomic instability .

• Acute sensitivity to ionizing radiation . • Predisposition to malignancy.

Amyotrophic Lateral Sclerosis(ALS)

• DEATH of → lower motor neurons in the spinal cord and brain stem → denervation of muscles, muscular atrophy (amyotrophy), weakness(Asymmetric Distal extremity weakness), and Fasiculations (Involuntary contractions of individual motor units).

Upper motor neurons in the motor cortex → Paresis, hyperreflexia, spasticity, along with a Babinski sign: The sole of the foot is stimulated with a blunt instrument → downward response (flexion) → negative
upward response (extension) → positive

• Most patients exhibits BOTH upper and lower motor neuron disease.
• 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.
• Eventually involves the Respiratory Muscles >>> recurrent bouts of pulmonary infection (the usual cause of death).
• 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 (Autosomal Dominant, early onset).
• Mutations in the Superoxide Dismutase Gene, SOD1, on chromosome 21 → Abnormal misfolded protein → apoptotic death of neurons → gliosis → Hardening (Sclerosis) .
• OTHER MUTATIONS:
• TDP43 (also associated with FTLD). • FUS gene.
• Hexanucleotide repeat expansion of C9orf72 (familial forms)

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.
• 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 (in case of bulbar).
• Sparing of those nerves supplying the extraocular muscles.
• Skeletal muscles show neurogenic atrophy.
• Cytoplasmic inclusions that contain TDP43 (genetic and clinical overlap with FTLD).

ACQUIRED METABOLIC AND TOXIC DISTURBANCES

Thiamine Deficiency

Causes:

• Chronic alcoholism, gastric disorders, gastric bypass surgery, or persistent vomiting.

Symptoms:

• Beriberi (Systemic Manifestations)
• Wernicke encephalopathy (Brain Manifestations)
• Abnormalities in eye movement(Nystagmus).
• Abrupt onset of confusion.
• Ataxia.

Treatment:

• Thiamine: reverses deficits
• Delayed Tx: IRREVERSIBLE profound Memory Disturbance (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 best correlates with the Memory Disturbance in Korsakoff syndrome.

Vitamin B12 Deficiency

Causes:

• Gastric sleeve , gastric bypass , autoimmune gastritis , pernicious anemia.

Symptoms:

• Symptoms develop over weeks.
• Anemia + neurologic deficits.
• Subacute combined degeneration of the spinal cord.
• Ascending and descending tracts of the spinal cord are affected.
• Early clinical signs:

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

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.

Hyperglycemia

• Often caused by Uncontrolled diabetes mellitus.

• Leads to either Ketoacidosis or hyperosmolar coma.

Symptoms:

• Confusion, stupor, and eventually coma.
• Intracellular dehydration.
• The correction must be gradual because Rapid correction can produce severe cerebral edema .

Hepatic Encephalopathy

• Hepatic dysfunction (or Cirrhosis) leads to depressed levels of consciousness or coma.
• Because diseased liver struggles to filter toxins such as ammonia , so → Elevated levels of ammonia, inflammation and hyponatremia.
• Ammonia metabolism occurs only in astrocytes “glutamine synthetase”.

Symptoms:

• Early stages: flapping tremor “asterixis”.

Microscopy:

• (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) :

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