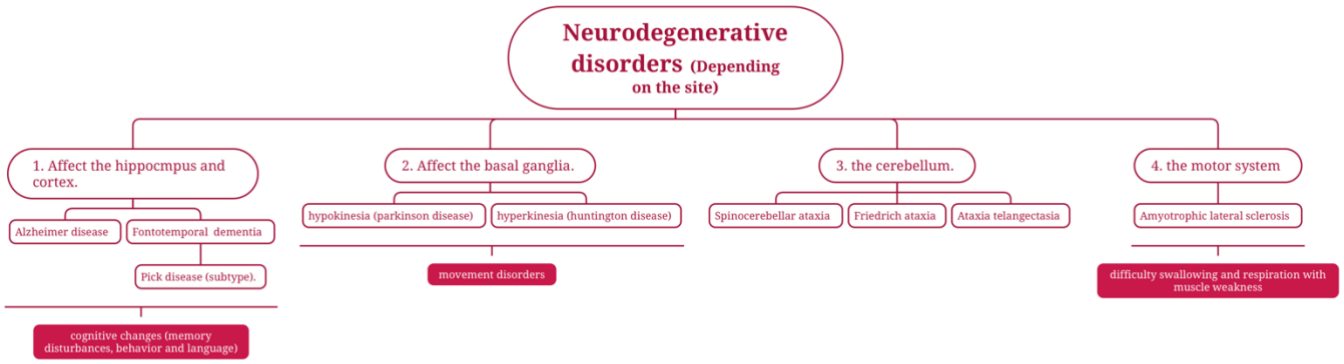
Neurodegenerative disorders

Lecture 1

- features of neurodegenerative diseases:
    1. affects groups of neurons with functional interconnections (different diseases ~> different neural system is involved ~> different symptoms).
    2. histologic hallmark ~> accumulation of protein aggregates (same protein may aggregate in different diseases but in different distribution).
    3. Protein aggregates can spread from one neuron to another in **Prion-like Pattern** (one aggregate leads to more aggregates).
    4. Proteins resist degradation ~> accumulation ~> inflammation (toxic to neurons).
    5. No person-to-person transmission.
    6. Activation of the **innate immune system**.
- Causes of protein accumulation: mutations that ~> 1. alter protein conformation OR 2. disrupting the processing and clearance of proteins or imbalance between protein synthesis and clearance (genetically or environmental).



Dementia:

- memory impairment and cognitive deficits (affect the person's performance in his daily life activities)
- The patient has **normal level of consciousness** with decreased capacity to function at his previous level.
- no standard normal cognition, always compared to previous level.

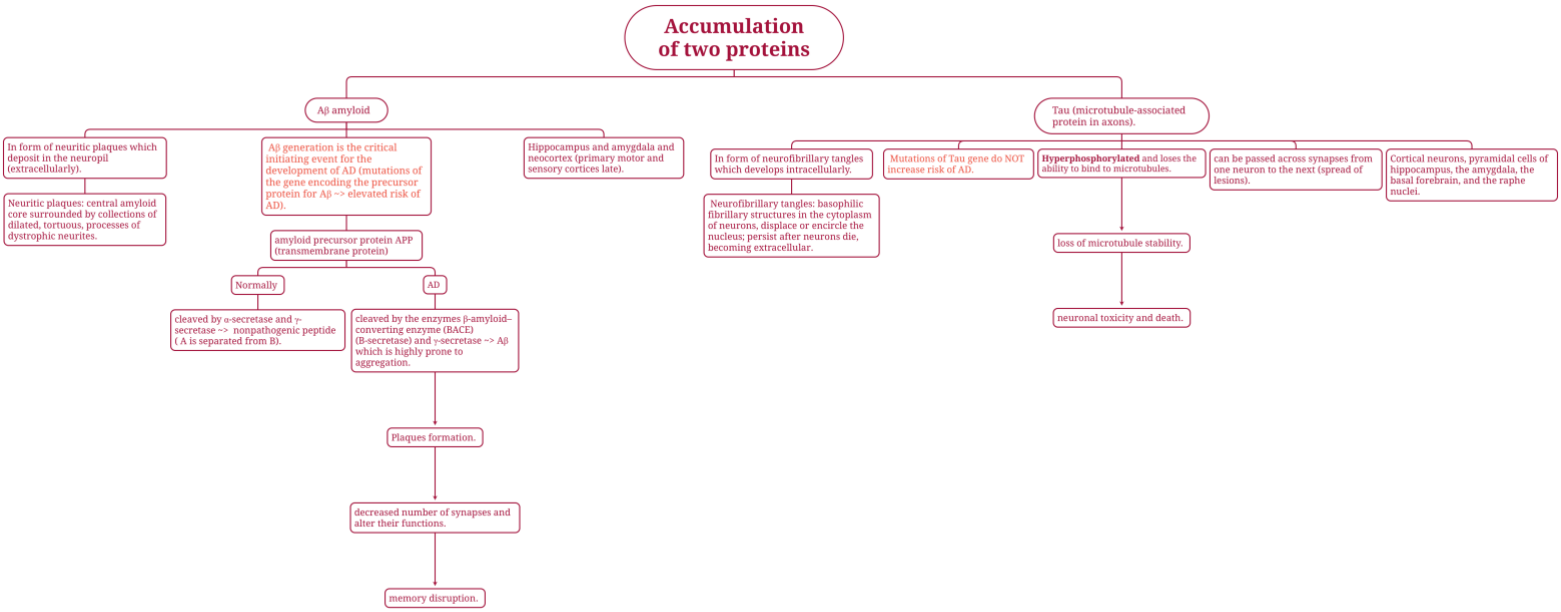
- Memory loss is usually noticed by some one else.

Neurodegenerative disorders

- Causes: neurodegenerative diseases, infections, nutritional deficiencies, metabolic and endocrine abnormalities, drugs, subdural hematoma, poisons, tumors, Anoxia and ischemia.
- Complications (مش مهم): inadequate nutrition (reduced or stopped), Inability to perform self-care tasks, personal safety challenges, death (**from infection**).

Alzheimer disease:

- Most common cause of dementia in older adults. With age ↑ (47% in those over 84).
- Mostly sporadic. 5-10% familial (< 50 years).
- Familial AD ~> mutations in APP or in components of γ-secretase.
- APP gene is located on chromosome 21 ~> increased risk in down syndrome.
- Symptoms: Impaired higher intellectual functions, memory impairment, altered mood and behavior, Severe cortical dysfunction with time (disorientation and aphasia, profound disability, mute and immobile), inability to acquire new memories and difficulty in recalling recently observed facts (most common). As the disease advances ~> symptoms include confusion, irritability and aggression, mood swings, language breakdown, long term memory loss, and ultimately a gradual loss of bodily functions and death.
- Death is due to **infections** (pneumonia): inflammatory response from microglia and astrocytes to Aβ and tau (innate immunity) ~> clearance of the aggregated peptide, and secretion of mediators that cause neuronal injury.



- Deposits of Aβ and tangles appear long before cognitive impairment (in familial before 15-20 years).
- ↑ plaques and tangles ~> severe cognitive dysfunction. (The number of neurofibrillary tangles correlates better with the degree of dementia than does the number of neuritic plaques)
- Morphine:

Neurodegenerative disorders

- Cortical atrophy (all neurodegenerative disorders), more marked atrophy seen superiorly and laterally.
- Sparing of the frontal lobe, at the beginning so behavioral changes are a late manifestation.
- Widening of the cerebral sulci.
- **Narrowed gyri with widened sulci.**
- frontal, temporal, and parietal lobes (occipital is NOT involved).
- Compensatory ventricular enlargement (hydrocephalus ex vacuo), due to Progressive cortical atrophy.

Frontotemporal Lobar Degeneration (type of dementia)

- Several disorders, affect the frontal and/or temporal lobes.
- Progressive deterioration of language and changes in personality which precede memory disturbances (opposite to AD).
- younger ages than AD.
- Two forms: 1. Contain tau. 2. Contain TDP43.
- Pick disease (subtype of FTLD-**tau**) ~> associated with smooth, round inclusions known as Pick bodies.
- TDP34 subtype (also deposited in ALS).
- Morphology:
  - Atrophy of frontal (from the beginning) and temporal lobes.
  - Neuronal loss and gliosis.
  - FTLD-tau ~> the characteristic neurofibrillary tangles, similar to AD.
  - Pick bodies in pick Disease.

Lecture 2

Parkinson Disease (PD):

- Second most common neurodegenerative disorder.
- **hypokinetic** movement disorder, caused by loss of **dopaminergic** neurons from the **substantia nigra**.
- Parkinsonism (clinical syndrome): any damage of dopaminergic neurons, which project from the **substantia nigra** to the striatum (control of motor activity).
- Parkinsonism: tremor, rigidity, bradykinesia, and instability.
- Parkinsonism can be induced by drugs such as dopamine antagonists or toxins that selectively injure dopaminergic neurons.
- Most cases sporadic, some are autosomal dominant (mutation of α-synuclein gene).
- protein accumulation and aggregation (abnormal protein and organelle clearance) ~> mitochondrial abnormalities and neuronal loss in the substantia nigra and elsewhere in the brain } Due to **defects in autophagy and lysosomal degradation**.
- Clue and diagnostic feature ~> **Lewy body**.

Neurodegenerative disorders

- Morphology: substantia nigra and locus ceruleus are pale (loss of the pigmented (catecholaminergic) neurons), gliosis, Lewy bodies, Lewy neurites.
    - Lewy bodies: neuronal inclusions containing α-synuclein, a protein involved in synaptic transmission. cytoplasmic, eosinophilic, round to elongated inclusions. ~> Immunohistochemical staining for α-synuclein (for lewy bodies).
    - Lewy neurites: dystrophic neurites that contain aggregated α-synuclein.
    - With progression involvement of medulla, pons, amygdala, and the cerebral cortex.
- Progresses over 10 to 15 years.
- Eventually ~> severe motor slowing or near immobility.
- dementia within 1 year of PD ~> Lewy body dementia.
- Death due to aspiration **pneumonia** or **trauma** from falls caused by postural **instability**.
- Symptomes:
    1. Tremor ~> involuntary shaking, usually **at rest and disappears with movement,** begins in a limb (hands or fingers), Patients might rub their thumb and forefinger back-and-forth (pill-rolling tremor).
    2. Slowed movement (bradykinesia) ~> shorter steps, difficult to get out of a chair, Patients drag their feet as they try to walk. (Shuffling, festinating gate)
    3. Rigidity ~> stiff muscles, painful, limit range of motion.
    4. Impaired posture and balance ~> stooped posture (leaning forward).
    5. Loss of automatic movements (blinking, smiling, swinging arms during walking).
    6. Speech changes ~> speak softly, quickly, slur or hesitate before talking.
    7. Writing changes (hard).
    8. Diminished facial expressions (**Masked facies**).
- Treatment: 1. L-dihydroxyphenylalanine (L-DOPA) (does not slow disease progression or reverse morphologic findings, become less effective). 2. deep brain stimulation.

Huntington Disease:

- Autosomal dominant.
- degeneration of the striatum (caudate and putamen).
- Chorea (characteristic) ~> Involuntary jerky movements of all parts of the body (writhing movements of the extremities).
- Early cognitive symptoms (characteristic) ~> forgetfulness and thought and affective disorders, severe dementia, Increase risk of suicide.
- Progressive, death after an average 15 years.
- CAG trinucleotide repeat expansions in huntingtin protein gene located on 4p16.3 (Polyglutamine). Normally alleles contain 11 to 34 copies of the repeat, in huntington disease number of repeats is increased (hundreds).
- Mutant protein is subject to proteolysis ~> fragments can form large intranuclear aggregates ~> toxic.
- Larger numbers of repeats ~> earlier-onset disease.
- Age of onset:40-50 (related to the length of CAG repeats).

Neurodegenerative disorders

- Anticipation: Further expansions of the CAG (glutamine-encoding) repeats during spermatogenesis~> **paternal** transmission ~> earlier onset in the next generation.
- Morphology:
  1. Macroscopic: small brain, atrophy of the caudate nucleus and the putamen, secondary atrophy of globus pallidus, atrophy in the frontal lobe, dilated lateral and third ventricles.
  2. Microscopic: severe loss of neurons and gliosis (neurons that mostly sensitive to disappear early ~> neurons that release γ-aminobutyric acid (GABA), enkephalin, dynorphin, and substance), Intranuclear inclusions of huntingtin protein.
- Strong correlation between degeneration in the striatum and severity of motor symptoms and between cortical neuronal loss and dementia.

Lecture 3

- **Ataxia:** disfunction in the parts of the nervous system that coordinate movement.
  - 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.
  - Ataxic gait: lack of proper coordination and muscle coordination in the legs, unsteady gait (stumble and fall), ambulation abnormalities.
  - Diagnostic tests: heel to shin test and finger to nose test.

Spinocerebellar ataxia:

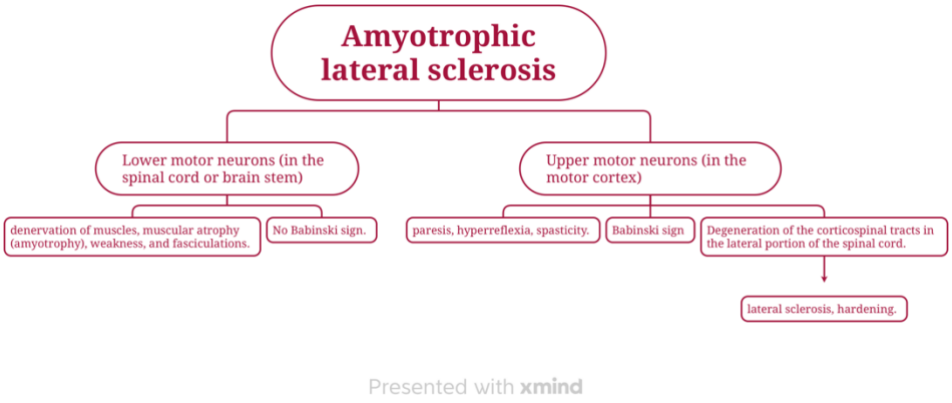
- Heterogeneous group of diseases.
- If cerebellar cortex is affected ~> sensory ataxia, if the spinal cord ~> spasticity, if the peripheral nerves (variably) ~> sensorimotor peripheral neuropathy. Other brain regions can be affected.
- Cerebellar atrophy.
- Mutation: CAG repeat expansions ~> several forms of SCA ~> intranuclear inclusions, among other mutations. (Some of SCA)
- **Friedreich ataxia**:
  - Most important SCA.
  - Autosomal recessive disorder.
  - First decade of life.
  - Symptoms: Gait ataxia, followed by hand clumsiness and dysarthria. Pes cavus (high arch of the foot) and kyphoscoliosis (kyphosis and scoliosis).
  - High incidence of cardiac disease and diabetes.
  - Mutations: GAA trinucleotide repeat expansion. Transcriptional silencing ~> decreased frataxin (regulates mitochondrial iron) ~> mitochondrial dysfunction>>oxidative damage (ROS).
- **Ataxia-telangiectasia**:
- Cerebella deterioration.
- Oculocutaneous telangiectasia.

Neurodegenerative disorders

- Immunodeficiency.
- Genomic Instability ~> predisposition to malignancy?
- Acute sensitivity to ionizing radiation.

Amyotrophic lateral sclerosis (ALS):

- Mostly sporadic.10% familial.
- Male predominance (>50 years).
- Mutations in the superoxide dismutase gene (**SOD1**), chromosome 21.
- The abnormal misfolded protein will trigger the unfolded protein response ~> apoptotic death of neurons.
- Most patients with both upper and lower motor disease.
- Sensation usually unaffected. cognitive impairment is not infrequent.
- subtle asymmetric distal extremity weakness ~ then~> muscle strength and bulk diminish ~eventually~> involves the respiratory muscles ~> recurrent bouts of pulmonary infection (the usual cause of death).



- Fasciculations: involuntary contractions of individual motor units.
- Bulbar amyotrophic lateral sclerosis (subtype): degeneration of the lower brain stem cranial motor nuclei. abnormalities of swallowing and speaking dominate.
- Morphology:
  1. Macroscopiy: the anterior roots of the spinal cord are thin and gray (most striking). atrophy of precentral gyrus; the motor cortex (sever cases).
  2. Microscopy: loss of of anterior horn neurons, reactive gliosis, loss of anterior root myelinated fibers (similar changes in motor cranial nerve nuclei), cytoplasmic inclusions that contain **TDP43**, skeletal muscles show neurogenic atrophy. With Sparing of nerves supplying the extraocular muscles.

Disease	Clinical pattern	Protein inclusion
AD	Dementia	Aβ, tau
FTLD	Behavioral changes, language disturbances	Tau, TDP43, others (rare)
PD	Hypokinetic	α-synucein, tau
HD	Hyperkinetic	Hungtingtin
SCA	Cerebellar ataxia	Various proteins
ALS	Weakness and lower and upper motor neurons signs	SOD1, TDP43

Acquired metabolic and toxic disturbances:

- Common causes of neurologic illnesses. Brain is vulnerable because of its high metabolic demands.
- **Thiamine Deficiency:**
  - Chronic alcoholism, gastric disorders, gastric bypass surgery, or persistent vomiting.
  - Systemic manifestations ~> Beriberi.
  - Neurologic manifestations ~> Wernicke encephalopathy.
  - Abrupt onset of confusion, ataxia, abnormalities in eye movement
  - Treatment: thiamine, if delayed ~> irreversible profound memory disturbance (Korsakoff syndrome).
  - Wernicke-Korsakoff syndrome.
  - Morphology: Foci of hemorrhage and necrosis (mammillary bodies and adjacent to the 3rd and 4th ventricles). cystic space with hemosiderin-laden macrophages (late). Medial dorsal nucleus of thalamus lesions (with the memory disturbance in Korsakoff syndrome).
- **Vitamin B12 deficiency:**
  - Subacute combined degeneration of the spinal cord (ascending and descending tracts).
  - Anemia + neurologic deficits.
  - Symptoms (over week): mild ataxia, lower-extremity numbness and tingling, spastic weakness of the lower extremities, complete paraplegia (poor outcome despite treatment).
- **Hypoglycemia:**
  - Resemble global hypoxia (anoxia).
  - **Hippocampal** neurons are particularly susceptible.
  - Cerebellar **Purkinje** cells are **spared**.
  - If sever ~> widespread injury.
- **Hyperglycemia:**
  - Uncontrolled diabetes mellitus. Ketoacidosis or hyperosmolar coma.
  - Confusion ~> stupor ~> coma.
  - Intracellular dehydration. Rapid correction can produce severe cerebral edema (correct gradually).
- Hepatic dysfunction ~> elevated levels of ammonia, with inflammation and hyponatremia.
  - Ammonia metabolism occurs only in astrocytes (glutamine synthetase), called Alzheimer type II cells.
  - Alzheimer type II cells: astrocytes in the cortex and basal ganglia with swollen pale nuclei because.
  - flapping tremor (asterixis) in early stages, depressed levels of consciousness or coma.

Neurodegenerative disorders

- **Acute intoxication (ethanol)**: reversible. Excessive intake ~> profound metabolic disturbances (brain swelling and death).
- **Chronic alcoholism**: cerebellar dysfunction. 1% of cases ~>atrophy in the anterior vermis. Truncal ataxia, unsteady gait, nystagmus.