Neurodegenerative disorders

• Progressive loss of neurons.
• The histologic hallmark for ALL diseases is the ACCUMULATION OF PROTEIN AGGREGATES(due to mutations that alter protein conformation ”abnormal shape eg. misfolded proteins”/ mutations disrupting the processing and clearance of proteins/ subtle imbalance between protein synthesis and clearance (genetic or environmental factors).
• Proteins resist degradation, accumulate within the cells, elicit inflammatory response and is toxic to neurons.
• Protein aggregates can spread from one neuron to another in Prion- like pattern.
• No evidence of person-to-person transmission (not infectious)
• Activation of the innate immune system is a common feature of neurodegenerative diseases.
• Same protein may aggregate in different diseases, BUT AT DIFFERENT DISTRIBUTION⟶ different symptoms

Different diseases according to the location:

1) Involving the cortex>>>> cognitive abnormalities of memory, behavior and language >>>>dementia(Occipital lobes are SPARED in dementia: NOT affected) >>>>>ALZHEIMER DISEASE (AD) , FRONTOTEMPORAL DEMENTIA (FTD), PICK DISEASE (SUBTYPE OF FTD).
2) Involving the basal ganglia >>>>> movement disorders >>>>hypokinesia (PARKINSON DISEASE) or hyperkinesia (HUNTINGTON DISEASE).
3) Involving the cerebellum >>>> ataxia >>> (SPINOCEREBELLAR ATAXIA, Friedrich ataxia, ataxia telangectasia).
4) Involving the motor system >>> difficulty swallowing and respiration with muscle weakness/paralysis >> (AMYOTROPHIC LATERAL SCLEROSIS).

DEMENTIA

• Memory impairment + other cognitive deficits(must affect the person’s performance in his daily life activities), despite NORMAL level of consciousness.
• Cognitive, psychological and motor symptoms.
• COMPLICATIONS OF DEMENTIA:
-Inadequate nutrition.
-Pneumonia. Difficulty swallowing increases the risk of choking or aspirating food into the lungs
-Inability to perform self-care tasks.
-Personal safety challenges.
• Coma and death.

Alzheimer disease (AD)

• Most common cause of dementia in older adults. • Gradual onset.

•Most cases are sporadic/ 5-10% are familial (onset before 50) ; inherited.

• Impaired higher intellectual functions, memory impairment(inability to acquire new memories & difficulty in recalling recently observed facts. Therefore he only mention old memories.) and altered mood and behavior.

• There is sparing of the frontal lobe, at least at the beginning so behavioural changes are a late manifestation.

• Severe cortical dysfunction (disorientation and aphasia, profound disability, mute and immobile).

• Death usually due to infections (pneumonia).

Morphology:

• Cortical atrophy → Compensatory ventricular enlargement (hydrocephalus ex vacuo)

•Narrowed gyri & widened sulci.

• Most pronounced in the frontal, temporal, and parietal lobes.

• More marked atrophy seen superiorly and laterally, with sparing of the occipital region.

Pathogenesis:

• Accumulation of → AB amyloid → Neuritic plaques (an extracellular lesion, in neuropil): central amyloid core surrounded by collections of dilated, tortuous, processes of dystrophic neurites.

➢ Their distribution: Hippocampus, amygdala and neocortex, (relative sparing of primary motor and sensory cortices until late).

Tau → ➢Neurofibrillary tangles (develops intracellularly): basophilic fibrillary structures in the cytoplasm of neurons, displace or encircle the nucleus; persist after neurons die, becoming extracellular.

• Hyperphosphorylated tau.

➢ Their distribution: Cortical neurons, pyramidal cells of hippocampus, the amygdala, the basal forebrain, and the raphe nuclei.

• Mutations of the gene encoding the precursor protein for Aβ (initiating event for the development of AD) >>> elevated risk of AD.

• Mutations of Tau gene (NOT the initiating event) do NOT increase risk of AD.

Frontotemporal Lobar Degeneration (FTLD)

• The onset of symptoms occurs at younger ages than for AD.

• Affects only frontal and temporal lobes.

• Progressive deterioration of language and changes in personality.

• Frontal lobe is affected from the beginning → Behavioral and language problems precede memory disturbances

• Accumulation of Tau and TDP43

Morphology:

• Atrophy of frontal and temporal lobes.

• Neuronal loss and gliosis

• In FTLD-tau, the characteristic neurofibrillary tangles, similar to AD .

• Pick disease (subtype of FTLD-tau), associated with smooth, round eosinophilic inclusions found in the cytoplasm of the neurons known as Pick bodies.

• The inclusion of TDP43 comes with the same symptoms and manifestations of Tau.

Role of Aβ:

• The transmembrane protein (amyloid precursor protein APP) is normally cleaved by α-secretase and γ-secretase → nonpathogenic peptide.

• when APP is sequentially cleaved by the enzymes β-amyloid–converting enzyme (BACE) (B-secretase) and γ-secretase → Aβ

• Mutations in APP or in components of γ-secretase lead to familial AD.

• The APP gene is located on chromosome 21, increased risk (happen at EARLIER age) in down syndrome (chromosome 21 mutation).

• Once generated, Aβ is highly prone to aggregation >>>> PLAQUES FORMATION >>> decreased number of synapses and alter their function (synapse transmission)>>> memory disruption and neural loss.

Role of tau:

• Tau is a microtubule-associated protein present in the axons.

• Responsible for tangles in AD >>> Tau aggregates leads to cell death.

• Hyperphosphorylated Tau → loses the ability to bind to microtubules >>>> loss of microtubule stability >>> neuronal toxicity and death.

• Tau aggregates can be passed across synapses from one neuron to the next >>> spread of lesions.

Role of inflammation:

• Innate immune system responds to Aβ and tau.

• Deposits of Aβ elicit an inflammatory response from microglia and astrocytes.

• Clearance of the aggregated peptide, and secretion of mediators that cause neuronal injury over time.

Basis for cognitive impairment:

• Deposits of Aβ and tangles appear before cognitive impairment by 10-15 yrs.

• Large burden of plaques and tangles is strongly associated with severe cognitive dysfunction.

• The number of neurofibrillary tangles correlates better with the degree of dementia than does the number of neuritic plaques.

• Immunohistochemical stain is used to show the AB plaques & the Tau tangles.

• If we want to spot the plaques, we should either use IHC stain or Congo-red stain (contains amyloid), the H&E stain used in this section CAN'T unravel the plaques.