Alzheimer disease

- Most cases are sporadic
- 5-10% are familial (onset before 50)
- Gradual onset
- Cognitive abnormality of memory, behavior and language
- The most commonly recognized symptom of Alzheimer is an inability to acquire new memories and difficulty in recalling recently observed facts
- Pathogenesis: Accumulation of two proteins (Aβ amyloid and Tau)

Aβ amyloid	**Tau**
form plaques	form neurofibrillary tangles (basophilic)
deposit in the neuropil	deposit intracellularly
critical initiating event for the development of AD	Mutations of Tau gene do NOT increase risk of AD
increased risk in down syndrome	
decreased number of synapses and alter their function	leads to cell death
elicit an inflammatory response from microglia and astrocytes	
In Hippocampus and amygdala and neocortex	In Cortical neurons, pyramidal cells of hippocampus, the amygdala, the basal forebrain, and the raphe nuclei
Congo red stain	Silver stain

- Deposits of Aβ and tangles appear before cognitive impairment
- The number of neurofibrillary tangles correlates better with the degree of dementia than does the number of neuritic plaques
- Sparing of the frontal lobe, at least at the beginning so behavioural changes are a late manifestation
- Morphology: Cortical atrophy/ Widening of the cerebral sulci/ ventricular enlargement (hydrocephalus ex vacuo)

Frontotemporal Lobar Degeneration (FTLD)

- Progressive deterioration of language and changes in personality
- Behavioral and language problems precede memory disturbances, in contrast to AD
- Frontal is affected from the beginning so patients present with behavioural problems first
- The onset of symptoms occurs at younger ages than for AD
- Neuronal inclusions, which may contain tau (similar to AD) or TDP43

- Pick disease (subtype of FTLD-tau), associated with smooth, round inclusions known as Pick bodies

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Parkinson Disease

- Second most common neurodegenerative disorder after Alzheimer's disease
- Hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the substantia nigra [Depigmented substantia nigra]
- Most cases sporadic, some are autosomal dominant (mutation of α-synuclein gene)
- Abnormal protein clearance due to defects in autophagy and lysosomal degradation
- Clue and diagnostic feature: Lewy body containing α-synuclein
- Lewy body dementia LBD ⟶ progression changes appear in: medulla, pons, amygdala, and the cerebral cortex.
- Initially respond to (L-DOPA), but this treatment does not slow disease progression or reverse morphologic findings
- SYMPTOMS:

1. Tremor: rest tremor / pill-rolling tremor
2. Slowed movement (bradykinesia): Shuffling , festinating gate
3. Rigid muscles/ Speech changes/ Writing changes/ Masked facies
4. Loss of automatic movements.: decreased ability to perform unconscious movements
5. Impaired posture and balance. stooped posture (leaning forward), and balance problems

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Huntington Disease

- Hyperkinetic movement disorder/ degeneration of the striatum (caudate and putamen)
- Autosomal dominant
- Pathogenesis: CAG trinucleotide repeat expansions in huntingtin protein gene
- Normal alleles contain 11 to 34 copies of the repeat
- Mutant protein is subject to proteolysis ⟶ fragments can form large intranuclear aggregates ⟶ toxic
- Age of onset: 40-50 years (more repeats; earlier age of onset)
- Atrophy of the caudate nucleus/ putamen/ globus pallidus
- Dilated lateral and third ventricles
- Involuntary jerky movements of all parts of the body [chorea]
- Early cognitive symptoms