Parkinson Disease (PD)

• A hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the substantia nigra
• Second most common neurodegenerative disorder after Alzheimer's disease.
• Parkinsonism → clinical syndrome: resting tremor, rigidity, bradykinesia, and instability.
↓
(NOT Parkinson's disease) : induced by drugs such as dopamine antagonists or toxins that selectively injure dopaminergic neurons.

Morphology:

• Pallor of the substantia nigra and locus ceruleus (depigmented).
• Loss of the pigmented neurons in these regions.
• Gliosis.
• Lewy neurites: dystrophic neurites contain aggregated α-synuclein.
• The disease starts in the basal ganglia but with progression changes can appear in: medulla, pons, amygdala, and the cerebral cortex (+ cognitive symptoms → Lewy body dementia LBD).

Pathogenesis:

• Protein accumulation, mitochondrial abnormalities and neuronal loss in the substantia nigra and elsewhere in the brain.
• Abnormal protein and organelle clearance due to defects in autophagy and lysosomal degradation.
• Clue and diagnostic feature: Lewy body (neuronal inclusions containing α-synuclein, a protein involved in synaptic transmission), they are intra-cytoplasmic, rounded, eosinophilic (pink in color on H&E stain) unless we used an immunostain for the alpha synuclein, they will appear as brown bodies.
• Most cases sporadic, some are autosomal dominant (mutation of α-synuclein gene).

Huntington Disease

• (Inherited) autosomal dominant movement disorder associated with degeneration of the striatum (caudate and putamen).
• Involuntary jerky movements of all parts of the body (chorea); writhing movements of the extremities .
• Early cognitive symptoms –unlike Parkinson- (forgetfulness and thought and affective disorders, mental retardation and severe dementia).

Morphology:

• Brain is small
• Striking atrophy of the caudate nucleus and the putamen
• Atrophy of globus pallidus
• Dilated lateral and third ventricles
• Severe loss of neurons from affected regions of the striatum + gliosis.
• Spiny neurons that release γ-aminobutyric acid (GABA), enkephalin, dynorphin, and substance P are especially sensitive, disappearing early.
• Intranuclear inclusions (aggregates of ubiquitinated huntington protein).

Pathogenesis:

• CAG trinucleotide repeat expansions in huntington protein gene located on 4p16.3 (Polyglutamine)
• Normal alleles contain 11 to 34 copies of the repeat (35 and more is characteristic for Huntington's disease).
• Disease-causing alleles, number of repeats is increased → earlier age of onset disease.

Clinical Features:

• Severe motor slowing or immobility.

• Death due to aspiration pneumonia or trauma from falls caused by postural instability.

• Initially respond to L-dihydroxyphenylalanine (L-DOPA), but this treatment does not slow disease progression or reverse morphologic findings.

• Over time, L-DOPA becomes less effective.

• Another Tx: deep brain stimulation.

Symptoms:

• Tremor: involuntary shaking, usually at rest and disappears with movement, begins in a limb, often in the hands or fingers. Patients might rub their thumb and forefinger back-and-forth (pill-rolling tremor).

• Bradykinesia: short steps, Shuffling , festinating gate.

• Rigidity: The stiff muscles can be painful and limit the range of motion.

• Impaired posture and balance, stooped posture (leaning forward).

• Loss of automatic movements.: decreased ability to perform unconscious movements, including blinking, smiling or swinging arms during walking.

• Speech changes: Patients might speak softly, quickly, slur or hesitate before talking.

• Writing changes. It may become hard to write.

• Diminished facial expressions (Masked facies).

• Mutant Huntington's protein is subject to proteolysis >>> fragments can form large intranuclear aggregates >>> toxic.