Neurodegenerative Diseases (2)

Neurodegenerative diseases according to the location:

1. Diseases involving the **hippocampus** and **cortex** >>>> cognitive changes (memory disturbances, behavior and language) >>>> dementia >>>>> Alzheimer Disease (AD), Frontotemporal Dementia (FTD), Pick Disease (subtype of FTD)

2. Diseases involving the **basal ganglia** >>>>> movement disorders >>>> hypokinesia (Parkinson Disease) OR hyperkinesia (Huntington Disease)

3. Diseases involving the **cerebellum** >>>> ataxia >>> (Spinocerebellar Ataxia, Friedrich Ataxia, Ataxia Telangiectasia)

4. Diseases involving the **motor system** >>> difficulty swallowing and respiration with muscle weakness >> (Amyotrophic Lateral Sclerosis)

Diseases involving the basal ganglia

1st 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 ≠ Parkinson Disease)

  - Parkinsonism is a clinical syndrome: tremor, rigidity, bradykinesia, and instability.

  - Parkinsonism: any damage of dopaminergic neurons, which project from the substantia nigra to the striatum (which are the control of motor activity).

  - Parkinsonism: induced by drugs such as dopamine antagonists or toxins that selectively injure dopaminergic neurons.

- Pathogenesis:

- **Protein accumulation** and aggregation, **mitochondrial abnormalities**.
- Abnormal protein and organelle clearance due to **defects in autophagy and lysosomal degradation**.

  >>> Neuronal loss in the substantia nigra and elsewhere in the brain.

- Clue and diagnostic feature:

- **Lewy body** (neuronal inclusions containing **α-synuclein**, a protein involved in synaptic transmission).

- Most PD cases are **sporadic**; some are **autosomal dominant** (mutation of α-synuclein gene).

- Morphology:

1. Pallor of the **substantia nigra** and **locus ceruleus** due to (1) loss of the pigmented (catecholaminergic, dopaminergic) neurons in these regions and (2) gliosis.
2. Lewy bodies in neurons (cytoplasmic, eosinophilic, round to elongated inclusions).
3. Lewy neurites: dystrophic neurites that also contain aggregated α-synuclein. (neurites = processes)

- We use immunohistochemical staining for α-synuclein (for subtle Lewy bodies).

- With progression, involvement of: **medulla**, **pons**, **amygdala**, and the **cerebral cortex** (causes Lewy Body Dementia)

- Clinical Features:

- Progresses over 10 to 15 years (gradual onset of symptoms).

- Eventually: severe motor slowing or near immobility.

- Lewy body dementia develops within 1 year of PD due to cerebral cortex involvement.

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

- Treatment (Tx):

- Initially respond to L-dihydroxyphenylalanine (**L-DOPA**), but this treatment does not slow disease progression or reverse morphologic findings. Over time, becomes less effective.

- Another Tx: **deep brain stimulation**

- Symptoms:

1. **Resting 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**).
2. **Slowed movement (bradykinesia)**: steps may become shorter, difficult to get out of a chair. Patients drag their feet as they try to walk. (**Short steps** + **Shuffling, festinating gate**).
3. **Rigid muscles (rigidity)**: The stiff muscles can be **painful** and limit the range of motion.
4. **Impaired posture and balance:** leaning forward posture (**Stooped posture**).
5. **Loss of automatic movements**: decreased ability to perform unconscious movements, including blinking, smiling or swinging arms during walking.
6. **Speech changes:** Patients might speak softly, quickly, slur or hesitate before talking.
7. **Writing changes:** It may become hard to write.
8. **Diminished facial expressions** (**Masked facies**).
9. **Slow voluntary movement.**

2nd Huntington Disease

- **Autosomal dominant** movement disorder associated with degeneration of the **striatum (caudate and putamen)**.

- Clinical Features:

  - Involuntary jerky movements of all parts of the body; writhing movements of the extremities **(Chorea)**.

  - Early cognitive symptoms (forgetfulness and thought and affective disorders, severe dementia).

  - Increase risk of suicide.

  - Progressive, death after an average 15 years.

- Pathogenesis:

  - **CAG trinucleotide repeat expansions in huntingtin protein gene** located on 4p16.3 (Polyglutamine).

    - Normal alleles contain 11 to 34 copies of the CAG repeat.

    - Disease-causing alleles: number of repeats is increased (may be hundreds).

  - Age of onset: 40-50 years, **larger numbers of CAG repeats result in earlier-onset disease**.

  - Mutant protein accumulation >>> Aggregates >>> Neuronal cells loss.

  - Spiny neurons (Striatal neurons) that release γ-aminobutyric acid (**GABA**), **enkephalin**, **dynorphin**, and **substance P** are especially sensitive, disappearing early.

  - Anticipation: Further expansions of the CAG (glutamine-encoding) repeats during spermatogenesis >>> (Paternal transmission (from father to son)) >>> earlier onset in the next generation.

- Morphology:

- Macroscopically:

1. Brain is small (atrophied).
   - Striking atrophy of the **caudate nucleus** and the **putamen**
   - Secondary atrophy of **globus pallidus**
   - Atrophy frequently also is seen in the **frontal lobe**.
2. Dilated lateral and third ventricles (due to atrophy of the head of the caudate nucleus).

- Microscopically:

1. Severe loss of neurons in affected regions of the striatum + gliosis in these regions.
2. Intranuclear inclusions (aggregates of ubiquitinated huntingtin protein)

- Strong correlation between degeneration in the striatum and severity of motor symptoms; and between cortical neuronal loss and dementia.

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Summary

Parkinson Disease

- Definition: **Hypokinetic** movement disorder resulting from the loss of dopaminergic neurons in the **substantia nigra**.

- Epidemiology: Second most common neurodegenerative disorder.

- **Parkinsonism**:

  Clinical syndrome characterized by tremor, rigidity, bradykinesia, and instability. Caused by dopaminergic neurons abnormalities, including:

  1. **Parkinson disease** itself.
  2. Induced by **drugs** such as dopamine antagonists or **toxins** that selectively injure dopaminergic neurons.

- Pathogenesis:

  Protein accumulation (**alpha-synuclein**), mitochondrial abnormalities, and defective protein/organelle clearance >>> Neuronal cells loss.

- Diagnostic Clue: Presence of **Lewy bodies** containing α-synuclein (a protein involved in synaptic transmission).

- Clinical Features:

  Gradual onset of symptoms progressing over 10 to 15 years, including resting tremor (pill-rolling tremor), bradykinesia (shuffling, festinating gate), rigidity, stooped posture, loss of automatic movements, speech changes, and masked face.

- Most cases are **sporadic**; some are **autosomal dominant**.

- Morphology:

  1. Substantia nigra loses its dark pigmentation (pallor).
  2. Lewy bodies are intracytoplasmic, rounded, eosinophilic. Can be stained by ubiquitin immuno-stain.

- Disease can spread to involve medulla, pons, amygdala, cerebral cortex leading to **Lewy body dementia**.

- Treatment:

  - Initially responsive to **L-DOPA**, but becomes less effective over time; **deep brain stimulation** is an alternative therapy.

Huntington Disease

- Definition: **Autosomal dominant hyperkinetic** disorder associated with degeneration of the **striatum (caudate and putamen)**.

- Clinical Features: Involuntary jerky movements (Chorea), cognitive symptoms (unlike Parkinson disease, cognitive symptoms appear early) and increased risk of suicide.

- **Chorea** (dancing movements) and **Athetosis** (snake-like movements) is a hallmark in this disease.

- Pathogenesis:

  Caused by CAG trinucleotide repeat expansions in the huntingtin protein gene (4p16.3), leading to mutant protein accumulation >> aggregates formation >> Neuronal loss.

    - Normal alleles have 11 to 34 copies of CAG trinucleotide.

    - Disease causing alleles may have hundreds of copies of CAG trinucleotide.

- Age of Onset: Between 40-50 years, **earlier onset with larger CAG repeat expansions**.

- Anticipation: Further expansions of CAG repeats during spermatogenesis result in earlier onset in subsequent generations.

- Morphology:

1. Atrophy of caudate nucleus, putamen, globus pallidus and frontal lobe.
2. Enlargement in lateral and third ventricles.
3. Intranuclear inclusions of ubiquitinated huntingtin protein.