Unit VIII – Problem 5 – Pathology: Parkinsonism

- **Parkinsonism = the clinical syndrome of Parkinson's disease.**
- **Parkinson's disease has variable etiologies:**
  - 70% of the cases are primary/idiopathic (unknown reason).
  - There is secondary or acquired Parkinsonism.
  - Hereditary Parkinsonism.
  - Parkinson plus syndromes: in which other parts of the central nervous system will be involved.
- **Clinical manifestations of Parkinson's disease:**
  - Rigidity (lead-pipe and cog-wheel).
  - Diminished facial expressions (mask-face)
  - Pin rolling tremor (tremor at rest).
  - Shuffling gait (festinating gait).

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PRIMARY PARKINSONISM

- Dopaminergic neurons of substantia nigra pars compacta (which is considered as part of the basal ganglia) will be degenerated due to the formation and accumulation of an abnormal protein (alpha-synuclein) bound to ubiquitin.
  - Notice that the protein which is produced might be normal but there is a lysosomal defect or any other defect which is inhibiting its degradation. Therefore, it will not be removed from cell body leading to its accumulation (in increased levels) → this is another mechanism of the disease.
- **Lewy body**: it is an abnormal accumulation of an abnormal protein known as alpha-synuclein. It is formed in:
  - Neuronal processes.
  - Astroglial cells.
  - And oligodendrocytes.

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SECONDARY PARKINSONISM

- This was discovered when a drug addict accidentally injected himself with synthetic heroin contaminated with MPTP (1-methyl-1-4-phenyl-1,2,3,6-tetrahydropyridine).
- The active compound of MPTP is MPP (1-methyl-4-phenylpyridinium) leading to damage of dopaminergic neurons and resulting in symptoms similar to Parkinson's disease.

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HERIDITARY PARKINSONISM

- **Genes which are identified are:**
  - **Alpha-synuclein (SNCA).**
  - Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1).
  - Parkin (PRKN).
  - **Leucine-rich repeat kinase 2 (LRRK2)**

  Note: those with red color are the most important two genes.

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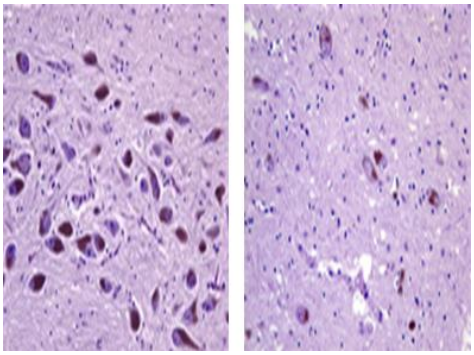
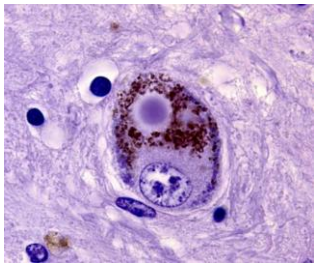
MORPHOLOGY OF PARKINSON'S DISEASE

- **Right**: pigmented substantia nigra in a normal person. **Left**: depigmented substantia nigra seen in patients with Parkinson's disease.



- **Left**: normal because of the presence of pigmented dopaminergic neurons. **Right**: abnormal because there is a loss of dopaminergic neurons.



- **Lewy body**: eosinophilic body surrounded by a hollow ring and the pigment.

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PARKINSON PLUS SYNDROMES

- **They are not responding to the usual treatment of Parkinson's disease so the prognosis is worse. They are characterized by the accumulation of 2 types of proteins:**
  - **Alpha-synuclein:**
    - ✓ Multiple system atrophy:
      - ❖ Occurring when there are features of parkinsonism with autonomic failure, cerebellar dysfunction and pyramidal signs (involvement of other systems).
      - ❖ Alpha-synuclein is present in oligodendrocytes and microglial cells (not in neurons and astrocytes as in idiopathic parkinsonism).
      - ❖ Inclusions are known as glial cytoplasmic inclusions (not Lewy bodies as in idiopathic parkinsonism). These inclusions are rich in iron & ferritin.
    - ✓ Diffuse Lewy body disease:
      - ❖ It is diffuse in brain parenchyma not only in substantia nigra.
      - ❖ Overlapping clinically with Alzehimer's disease (in which there is loss of cholinergic neurons) & Parkinson's disease (in which there is loss of dopaminergic neurons).
      - ❖ The cerebral cortex degenerates.
  - **Or tauproteins:**
    - ✓ Progressive supranuclear palsy:
      - ❖ There will be manifestations of parkinsonism with paralysis of vertical eye movements, truncal rigidity, postural instability, mild dementia, abnormal speech and pseudo-bulbar palsy.
      - ❖ Electron microscope: 15 mm nanometer filaments composed of tau-proteins in glial cells & neurons.
    - ✓ Corticobasal ganglionic degeneration (CBGD):
      - ❖ There is cortical atrophy especially in frontal and parietal lobes.